1-22-80
Vol. 45—No. 15
BOOK 2
PAGES
5001-5296

federal register

Book 2 of 2 Books
Tuesday, January 22, 1980

Part VII

Department of Labor

Occupational Safety and Health Administration

Identification, Classification and Regulation of Potential Occupational Carcinogens

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

29 CFR Part 1990

Identification, Classification and Regulation of Potential Occupational Carcinogens

AGENCY: The Occupational Safety and Health Administration of the United States Department of Labor (OSHA).

ACTION: Final rule.

SUMMARY: This Part, promulgated today, sets forth OSHA's general policy for the identification and regulation of physical and chemical substances that pose a potential occupational carcinogenic risk to humans. The Part provides for future individual rulemakings concerning each substance, or combination or mixture of substances, or process to be regulated, thereby affording the public and OSHA the opportunity, among other things, to determine the applicability of this general policy to any specific substance, combination or mixture of substances or process and to select the most effective type of regulation to control human exposures to such potential occupational carcinogenic substance, combination or mixture of substances or process.

EFFECTIVE DATE: April 21, 1980.

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I. INTRODUCTION

A. THE FORMAT OF THIS STATEMENT OF REASONS (THE PREAMBLE)

In addition to the Table of Contents and this Introduction, this document consists of four other major components. Part A explains the rationale for and the necessity of the promulgation today of this general policy and procedure of the Occupational Safety and Health Administration (OSHA), a policy and procedure which describe how potential occupational carcinogens will be identified, classified and regulated in the future unless good grounds exist for deviation from that general policy.

Part B of this document describes those issues underlying this rulemaking that are involved in the use of evidence derived from the human experience in the qualitative scientific and policy determinations of whether a substance, or combination of substances, poses a potential carcinogenic hazard to humans, namely whether exposure to such substance or substances should be regarded as having some potential for increasing the risk of cancer to humans. Part B also describes those scientific and policy issues that are involved in the methods (and assumptions on which they are based) for attempting to estimate, when appropriate, the magnitude of that risk in exposed human populations. Part C describes the same issues as Part B except that it deals with the use of evidence derived from experimentation in mammalian laboratory animals.

Other relevant scientific issues not disposed of in Parts B and C and issues of a policy or legal nature are discussed in Part D. In addition, Part D also includes a description of the procedural mechanisms set forth in this final set of regulations and any additional rationale not already discussed. A bibliography of some of the scientific and other publications referred to in this Statement of Reasons is also included. Part E consists of the Regulatory text.

References to the direct written testimony of witnesses are designated by the name of the witness, the letter "S" and the page of the statement, *e.g.*, Upton, S. 5. References to the oral direct testimony or questioning of any witness are preceded by the witness's nan... and the general transcript page number, *e.g.*, Upton, Tr. 450. In addition, the federal agency, state agency, university, employer or participant affiliation is noted where applicable, *e.g.*, Upton (Director, NCI), S. 5 or Upton (Director, NCI), Tr. 450. Exhibits admitted to the Record of the public hearing are referred to by exhibit number, and also by author and date if they are publications in the scientific literature. Other scientific publications referred to by witnesses are also cited by author and date.

B. DESCRIPTION

Pursuant to sections 6(b), 8(c) and 8(g) of the Occupational Safety and Health Act of 1970 (the Act) (84 Stat. 1593, 1599, 29 U.S.C. 655, 657), the Secretary of Labor's Order 8–76 (41 FR 25059) and Title 29 of the Code of Federal Regulations (CFR), Part 1911, Title 29 of the CFR hereby is amended by adding a new Part 1990, to deal with the specific identification, classification and regulation of toxic substances for which there is reported to be evidence of a carcinogenic potential to humans. In addition, The Part sets forth some of the factors which OSHA will normally consider in establishing priorities. As discussed below, these regulations generally apply to all employments in all industries covered by the Act, including general industry, construction, maritime and agriculture, as to the scientific identification and classification of potential carcinogens. (29 CFR 1990.101) However, the regulatory requirements for research laboratories and the construction, agriculture and maritime industries may involve different approaches, depending upon the industry involved.

This set of regulations promulgated today attempts to deal with one of the most important issues OSHA faces, namely the exposure of workers to toxic substances which may be potential carcinogens. OSHA recognizes that in regulating occupational exposure to potential carcinogens, many gaps remain in our knowledge of cancer, its causes or cures. Minimizing exposures to potential carcinogens and thus minimizing the incidence of the disease, however, can be relatively swift if proper procedures such as this set of regulations are in place. We believe that to wait for years for science to provide further depth of understanding to the complex issues of cancer causation or cure, without having today some consistent and workable system for the reduction or prevention of human exposures to those toxic substances for which there is evidence of a carcinogenic potential to workers, would be inconsistent with OSHA's statutory obligations and unacceptable to all. In this regard, it should be noted that this rulemaking is tinctured by two factors:

a. The problem of reconciling a fluid, developing *science* into a rational and efficient *legal/policy* regulatory context without creating a rigidity that would hinder the scientific approach or meaningful scientific advances; and

b. The desire for a consistent approach by all concerned, including the Federal government, to the regulation of potential carcinogens, whether they be found in the workplace, in the general environment, in food and drinking water or in consumer products.

OSHA believes that this document encompasses an orderly, comprehensive and scientifically flexible set of regulations to identify, classify and regulate potential carcinogens in American workplaces, hopefully in a relatively short period of time. It also sets forth factors that OSHA will normally consider in establishing priorities. This action is based upon five basic propositions, namely:

1. That OSHA should consider all meaningful scientific information in the regulation of specific substances.

2. That the term "carcinogen", although perhaps difficult to define as a matter of science, must be defined for purposes of overall regulatory activity with the knowledge that as meaningful scientific advances are made, these regulations will be quickly amended to reflect such advances.

3. That a toxic substance, scientifically identified as a carcinogen in a mammalian test system, as defined, is to be treated *as a scientific and a policy matter* as posing a carcinogenic risk to humans, unless scientifically sound and convincing evidence demonstrates otherwise for the substance under consideration.

4. That when OSHA is regulating a Category I potential carcinogen, as defined herein, the permissible exposure limits will be set as low as feasible. In cases where there are suitable substitutes that are found to be less hazardous to the worker, no occupational exposure to the toxic substance will be permitted. These determinations are to be made in the individual rulemakings conducted pursuant to this Part.

5. That when OSHA is regulating a Category II potential carcinogen, as defined herein, regulatory requirements will generally be of a different degree than those imposed by the regulation of a Category I potential carcinogen.

In short, utilizing the best available scientific knowledge, OSHA will determine whether a substance poses a carcinogenic risk to humans, in general, by relying upon scientifically evaluated evidence from human epidemiological studies, animal studies or both. The degree of conclusiveness of such data may permit regulation of the toxic substance as a Category I potential carcinogen or a Category II potential carcinogen. Substances which on the basis of a brief scientific review of available data are considered candidates for further scientific review and possible regulation under this Part will be placed on the "Candidate List of Potential Occupational Carcinogens". Two priority lists will be prepared—a Category I Potential Carcinogen list and a Category II Potential Carcinogen list. The Candidate list and the priority lists have no regulatory effect and do not represent a determination that any of the substances on these lists are, in fact, potential occupational carcinogens. Rather, these lists are necessary steps in setting priorities and in allowing for public input. Further review of the evidence may result in the removal of a substance from the lists or may trigger regulatory activity through the issuance of a proposal or, in appropriate circumstances, an emergency temporary standard to control exposure to the potential occupational carcinogen. Guideline model standards will be utilized to facilitate this process.

The scientific and policy concepts underlying this policy, although sometimes controversial, have been followed after extensive consideration and scientific debate in other rulemakings by OSHA and other regulatory agencies many times in the past. For example, see the preambles to OSHA's carcinogen standard applicable to 14 selected substances, 29 CFR 1910.1003–1910.1016 (39 FR 3758), *aff'd, Synthetic Organic Chemicals) Manufacturers Assn. v. Brennan* I 503 F.2d 1155 (3rd Cir., 1974) *cert. den.* 420 U.S. 973 (1975) and *Synthetic Organic Chemical Manufacturers Assn. v. Brennan* II 506 F.2d 385 (3d Cir. 1974) *cert. den. sub nom. Oil, Chemical and Atomic Workers v. Dunlop* 423 U.S. 830 (1975); the vinyl chloride standard, 29 CFR 1910.1017 (39 FR 35892) *aff'd. The Society of the Plastics Industry v. OSHA,* 509 F.2d 1301 (2nd Cir.) *cert. den. sub nom. Firestone Plastics Co. v. U.S. Dep't of Labor,* 421 U.S. 992 (1975); the inorganic arsenic proposal (40 FR 3392, 1975) and final standard 29 CFR 1910.1018 (43 FR 19584, 1978), appeal pending *ASARCO v. OSHA* (9th Cir. 1978); the coke ovens emissions proposal (40 FR 32268, 1975) and final standard, 29 CFR 1910.1029 (41 FR 46742, 1976), *aff'd, American Iron and Steel Institute v. OSHA* 577 F.2d 825 (3rd Cir. 1978), petition for certiorari pending.

In addition to previous OSHA regulatory decisions, the United States Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) of the United States Department of Health, Education, and Welfare, the United States Consumer Product Safety Commission (CPSC) and other governmental agencies and bodies have, in the past, made, or recommended, regulatory decisions based upon the same views expressed in this document. The views of such governmental agencies, including research agencies, are quoted throughout this document. See, for example, however:

a. *EPA*:

In Re Stevens Industries, et al., (37 FR 13369, June 30, 1972), *aff'd*

Environmental Defense Fund (EDF) v. EPA, (DDT), 489 F.2d 1247 (D.C. Cir. 1973); *In Re Shell et al.,* (39 FR 37265, Oct. 18, 1974), *aff'd, EDF v. EPA,* (Aldrin and Dieldrin) 510 F.2d 1292 (D.C. Cir. 1975); Presticide Registration, Reregistration and Classification Procedures (40 FR 28241, July 7, 1975 and codified in 40 CFR Part 164); *In Re Velsicol et al.,* (41 FR 7552, 1976) *aff'd, EDF v. EPA,* (Heptachlor and Chlordane) 548 F.2d 998 (D.C. Cir. 1976), *cert. den.* 431 U.S. 925 (1977); *In Re: The Toxic Pollutant Effluent Standard for PCBs* (42 FR 6531, Feb. 2, 1977) *aff'd EDF v. EPA* (PCBs) 598 F.2d 62 (D.C. Cir., 1978) and *Hercules, Inc., et al. v. EPA* (Toxaphene) 598 F.2d. 91 (D.C. Cir., 1978); Proposed National Emission Standards for Hazardous Air Pollutants; Policy and Procedures for Identifying, Assessing, and Regulation of Airborne Substances Posing a Risk of Cancer, 44 FR 58642 (Oct. 10, 1979).

b. FDA:

In re: Chloroform (proposal, 41 FR 15026–29, April 9, 1976 and final, 41 FR 26842–46, June 29, 1976); *In re Chemical Compounds in Food-Producing Animals: Proposed Criteria and Procedures for Evaluating Assays for Carcinogenic Residues* (44 FR 17069, March 20, 1979).

c. *CPSC:*

In re: Vinyl Chloride (39 FR 36576, Oct. 11, 1974) revised and reissued (43 FR 12308, March 24, 1978); *In re TRIS* (42 FR 18850, April 8, 1977) revised and reissued (42 FR 61621, Dec. 6, 1977); *In re Asbestos* (42 FR 63354, Dec. 15, 1977); *In re Benzene* (43 FR 21839, May 19, 1978); *Interim Policy and Procedure for Classifying, Evaluating, and Regulating Carcinogens in Consumer Products* (43 FR 25657, June 13, 1978) (withdrawn for technical reasons on April 23, 1979).

Thus, we believe that this Part creates a system for regulatory action, based on a broad consensus of scientific and regulatory opinion, which will create a uniform and reasonable response to the regulation of potential carcinogens; will permit OSHA to regulate such substances in a timely manner; and which sets forth the factors OSHA will normally consider in setting priorities for the regulation of such substances. The existing case-by-case approach, with its constant re-examination of already resolved scientific and policy issues, does not permit regulation of such substances in a timely and efficient fashion. Moreover, OSHA believes this approach is needed to overcome the administrative difficulties created by the case-by-case approach. We also believe that this system will provide a responsible and relatively speedy response to new scientific data concerning hazards and risks to humans; is completely compatible and consistent in its scientific underpinnings with the positions taken by other regulatory and research health agencies of this Nation; and will provide clearer guidance to American employers on the identification, classification and regulation of potential occupational carcinogens, now or in the future. As the President of Dow Chemical Co. testified: "We think we should have a logical, workable regulation that every company, whether responsible or not, should stick to" (Oreffice, Tr. 3200).

In issuing these regulations, OSHA is relying upon leading scientific evidence and opinions believed to reflect the scientific conclusions of individual cancer specialists and expert national and international cancer committees and agencies, as well as "experience gained under . . . other health and safety laws" (section 6(b)(5) of the Act). In such a task we recognize that we are operating "on the frontiers of scientific knowledge" *Industrial Union Department v. Hodgson,* 499 F.2d 467, 474, (D.C. Cir. 1974) but with a "command to act" *Ethyl Corp. v. EPA* 541 F.2d 1, 28 (D.C. Cir. 1975) and "a heavy burden" to explain when no action is taken *EDF v. EPA (PCBs)* 598 F.2d 62 (D.C. Cir. 1978).

This Part is essentially a statement of general policy regarding regulation of toxic substances which may pose a cancer hazard to workers. It provides that certain exceptions may be made to the policy where it is shown that unique circumstances exist. (29 CFR 1990.144) In addition, it provides for consideration of substantial new issues and/or substantial new evidence. (29 CFR 1990.145) And if, because of scientific breakthroughs or other good reason, it appears that all or part of the policy is no longer appropriate, these regulations will be amended. (29 CFR 1990.106) In this way, OSHA will be able to deal with potential carcinogens far more efficiently while providing flexibility for exceptions and scientific advances. OSHA encourages petitions for amendments to these regulations as conditions so warrant and has provided for a review of the appropriateness of these regulations on a periodic basis.

C. THE RULEMAKING

1. The Development of the Proposal

On January 19, 1977, the Assistant Secretary of Labor for OSHA formally transmitted for review and comment a draft of the proposed set of regulations and preamble, to the National Advisory Committee on Safety and Health (NACOSH), a standing advisory committee provided for by section 7(a) of the Act. In addition, the acting Assistant Secretary, on February 17, 1977, formally transmitted the same package to NIOSH with a request for "NIOSH's formal review of the document and all suggestions on how to improve it as soon as possible".

On April 18, 1977, the Director of NIOSH responded that: "we feel it is advisable that OSHA proceed expeditiously to publish this draft, for public comment, as a proposed carcinogen regulation or administrative policy". NIOSH further stated that: "it ha[d] a number of technical concerns which can be discussed as the formal rulemaking proceeds . . .".

In the meantime, NACOSH held several subcommittee meetings, which were duly announced in the **Federal Register,** to discuss the draft preamble and regulations. Full public participation was invited and written and oral views and presentations were consistently encouraged. (See, e.g. 42 FR 4554 [1/25/77]; 42 FR 14181 [3/15/77]; 42 FR 19936 [4/15/77].) The two relevant NACOSH subcommittees, one the subcommittee on Standards and the other on Policy and Budget, on April 5, 1977, adopted a position which was received and adopted by the full NACOSH committee on May 5, 1977. The resolution adopted by NACOSH stated:

"RECOMMENDATIONS ON PROPOSED REGULATION OF CERTAIN TOXIC MATERIALS

"Having reviewed the draft document 'Regulation of Certain Toxic Materials', we endorse OSHA's general attempt to deal with this difficult problem. In order to develop in the public forum the various factors, including certain legal and scientific issues, for a regulatory carcinogen policy to govern OSHA's administrative approach and to promote a degree of predictability, the draft proposal should be published in the **Federal Register** solely for the purpose of information gathering and that neither the document nor the process be engaged for a rulemaking purpose at this time. This recommendation is proposed since:

"1. The document can be adopted by OSHA as an administrative policy, and there should be such flexibility.

"2. The document, even if adopted as a policy through the rulemaking process, would not deprive due process challenges when subsequent standards are promulgated.

"3. The document identifies those issues upon which much debate has evolved and should continue, including the concept that some substances, although not always scientifically definable as carcinogens, must be addressed because of a regulatory obligation."

Issues which need to be expanded

1. address adequacy of classification system
2. address carcinogenicity of impurities and mixtures

3. expand discussion on "other than animal testing" routes
4. anatomic and metabolic fate
5. decision on rate retention issue

At the meeting on May 5, 1977, some members of the public such as the representative of the Synthetic Organic Chemical Manufacturers Association (SOCMA) "object(ed) to the statement in the recommendation that OSHA has the authority to adopt the proposal as an administrative policy and the implication that it should do so. In our view there is a serious question as to whether the proposal can legally be adopted as an administrative policy by OSHA without rulemaking."

In addressing these concerns on the Record, the NACOSH members stated that they believed further public comment was needed because "the subgroup did not feel that it, itself, was in a position to evaluate the scientific and technical aspects of the document" to make meaningful comments (NACOSH Tr. 126, May 5, 1977). However, the full committee made it clear that it would make no recommendation as to how OSHA should proceed, *viz:*

Dr. Ashford: I think [Dr. Imbus of Burlington Industries, Inc.] is right when he said that we left it open for OSHA's legal reading on whether or not to adopt it.

Mr. Sheehan: It would not come back to this Committee to make a determination as to whether it should be an administrative policy.

Dr. Ashford: I think the decision as to whether it should be an administrative policy or a 6(b) rulemaking is left to the Solicitor and OSHA. I think that is best left in their hands.

Mr. Sheehan: That is correct. (NACOSH Tr. 126.)

During the spring and summer of 1977, OSHA carefully reviewed the recommendations of both NIOSH and NACOSH. Because of the importance of the issues and in order to assure the fullest public participation in resolution of the issues, and maximum usefulness of the cancer policy once adopted, OSHA decided that it should commence this rulemaking with the full procedures provided for in section 6(b) of the Act. The publicly stated alternative was OSHA's belief that an internal pronouncement of policy which would affect substantive rights of interested parties might not be sustainable in the Courts, thus, in actuality, delaying its effective date in this important area by years.

On June 13, 1978, the Consumer Product Safety Commission issued a "cancer policy" scientifically similar to that encompassed in this rulemaking. It was issued as an "interim policy" without public rulemaking. (43 FR 25657) On September 12, 1978, Dow Chemical Company and 6 other plaintiffs, namely Diamond Shamrock Corp., Ethyl Corporation, PPG Industries, Inc., Stauffer Chemical Company, Vulcan Materials Company and Louisiana Chemical Association, brought an action to enjoin the CPSC from proceeding with the implementation of that policy. The basis for the action was plaintiffs' allegations that CPSC had failed to comply with 5 U.S.C. sections 553 (b) and (c) of the Administrative Procedures Act.

In support of their motion for an injunction, Dow Chemical and the six other plaintiffs stated on September 15, 1978:

"Shortly after the IRLG was formed, the Occupational Safety and Health Administration took the lead in exploring the scientific and regulatory problems associated with potential carcinogens. On October 4, 1977, OSHA proposed a broad approach to carcinogens which would classify substances based on relative risk and then proceed to evaluate means for reducing risks of harm. OSHA has recently held four months of hearings on the scientific and policy issues involved in this proposal.

"In the course of these extensive hearings, there has been a vigorous debate as to the classification of carcinogens, risk evaluation, and the appropriate regulatory response."

* * * * *

"While OSHA and other governmental bodies were attempting to grapple with the problem of carcinogens in a systematic and coordinated way, the CPSC decided to shortcut this process by announcing its own position on this subject."

* * * * *

"The CPSC has made no real effort to examine the serious scientific and regulatory issues behind the interim regulations. The preamble to the June 13, 1978 [CPSC] regulations consists of a single page [in the **Federal Register**] of background information. In contrast, the preamble to the OSHA proposal regarding carcinogens contained 36 pages [in the **Federal Register**] of detailed discussion of the underlying scientific literature and policy issues. The CPSC has apparently ignored all of these data and issues, and is seeking to implement its own private notions without subjecting them to public scrutiny." (Dow's Memorandum of Points etc., pp. 5–7.)

The Court granted Dow Chemical and the other plaintiffs an injunction less than 2 months later in *Dow Chemical et al.* v. *Consumer Product Safety Commission* 459 F. Supp. 378 (W.D.La. 1978) on the basis that it believed that the CPSC cancer policy was more than a general statement of policy but would affect substantial rights of persons and therefore rulemaking was required.

2. The Proposal

The OSHA proposal, which Dow Chemical and others almost one year later characterized as an attempt "to grapple with the problem of carcinogens in a systematic and coordinated way", was published in the October 4, 1977, issue of the **Federal Register** (42 FR 54148). It requested the submission of written comment from all interested persons on the variety of scientific, technical and procedural issues addressed or implicit in the proposal by no later than December 8, 1977 with all direct written testimony of witnesses to be filed by January 9, 1978, over 4 months after the proposal was published. Moreover, OSHA transmitted the proposal to over 100 major trade associations and unions inviting their active participation in the rulemaking. In addition, OSHA scheduled an informal hearing to commence on March 4, 1978 to provide an opportunity for additional presentation of evidence concerning the issues and to facilitate the conduct of this rulemaking (42 FR 54183).

The proposal requested that the public's witness statements and comments be filed prior to the filing of the direct testimony of witnesses invited by OSHA to testify, which was scheduled to occur on February 28, 1978 (42 FR 54183). By doing so, OSHA intended to clarify the issues so that they would all be addressed and not "passed like ships in the night". The goal was to compile the fullest Record possible for the decision makers, in this case both the Assistant Secretary of Labor for OSHA and the Secretary of Labor.

In November 1977, requests for extensions of time were received. On November 22, 1977, as published in the November 29, 1977 issue of the **Federal Register** (42 FR 60753), the Assistant Secretary extended the time deadlines set forth in the October 4, 1977 proposal and stated:

OSHA wishes to encourage debate on the numerous issues raised by the proposed regulations, while recognizing the need to proceed as expeditiously as possible. For that reason OSHA has decided to extend the period for filing written comments, data, views and arguments and other notices of intention to appear to January 30, 1978. Further OSHA also extends the time period for the submission of testimony and documentary evidence to be introduced by public witnesses at the hearing to January 30, 1978.

Because of these extensions of time for submission from interested parties, OSHA will file the testimony of its witnesses and make them available on or before March 15, 1978, rather than by February 28, 1978, as set forth in the original notice. These extensions require rescheduling of the public rulemaking

hearing to April 4, 1978, rather than March 14, as set forth in the original notice. The place of the hearing has also been changed to the Departmental Auditorium, Constitution Avenue between 12th and 14th Streets N.W., Washington, D.C.

In January 1978, however, requests for additional extensions of time were again received together with requests to permit the public the opportunity to reply to any testimony filed by witnesses that had been requested by OSHA. On January 24, 1978, as published in the January 27, 1978 issue of the **Federal Register** (43 FR 3729), the Assistant Secretary again extended the time requirements of the original proposal and provided an additional opportunity for the public to submit supplemental responses. Specifically, an additional three weeks were set aside so that any public participant could file witness statements and comments addressing any issues raised by the statements filed by witnesses requested by OSHA to testify and not raised in the proposal. The hearing was rescheduled to begin on May 16, 1978. No further requests for extensions of time were received and not one party to the proceedings availed itself of the opportunity to file additional or supplemental witness statements as provided.

3. The Response to the Proposal and the Hearings

At the outset, it should be pointed out that, in the proposed notice of rulemaking, OSHA stated that it expected that some might question the policy and scientific decisions inherent in the proposal as going too far, while others might contend that they did not go far enough (42 FR 54149). OSHA proposed that all concerned, however, should approach these issues in a spirit of co-operation and candor—and with the recognition that policy determinations in a legal framework could not be based solely upon scientific fact where such factual data were often incomplete. But, insofar as the central issue of whether exposure to potential carcinogens should be regulated, OSHA stated that it believed that the time had come to say that at least this issue had been resolved (42 FR 54149). In that regard, OSHA cited the "expert"* blue ribbon scientific Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens of NCI, which reported over nine (9) years ago in 1970 to the Surgeon General of the United States that:

"An effective program to protect man from the mass of environmental cancer hazards is within reach. No more time should be allowed to pass before the recommendations set forth in this report are applied to reality." (NCI Ad Hoc Committee, 1970, p. 8.)

It should be noted that five (5) of the eight (8) members of that committee and two (2) of the staff members testified or presented evidence in this rulemaking, namely: Dr. Umberto Saffiotti (NCI); Dr. Paul Kotin (Johns-Manville), Dr. William Lijinsky (FCRC: NCI); Dr. Marvin A. Schneiderman (NCI); Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska); Dr. Richard R. Bates (FDA, NIEHS); and Dr. Elizabeth K. Weisburger (NCI).

This rulemaking, as described below, may well be the most important single proceeding OSHA has ever had or will ever conduct in the future in this area. It interested major segments of the public such as the American Petroleum Institute (API) who "strongly support(ed) 'the need for a comprehensive and rational policy for the regulation of carcinogens in the workplace'." (API Brief, p. 1). API further stated "(d)espite the many problems API has with the specifics of OSHA's Proposal, OSHA has provided a useful forum for the broad discussion of issues that may prove helpful in ultimately deciding the uniquely difficult questions presented by the regulation of carcinogens." (API Brief, p. 1). It included full participation by organized labor such as the American Federation of Labor and Congress of Industrial Organizations (AFL–CIO), the United Steelworkers of America (USW), the International Brotherhood of Teamsters, the United Automobile Workers (UAW), and the Oil, Chemical and Atomic Workers (OCAW). It attracted participation by environmental groups such as the Environmental Defense Fund (EDF), the Natural Resources Defense Council (NRDC) and the Health Research Group (HRG). And it spawned a major new trade association, the American Industrial Health Council (AIHC) and chaired by the President of Dow Chemical Co. (Oreffice, S. 1). The stated objective of AIHC was "cooperating with government, labor, and the public in developing a sound policy for the control of exposures to carcinogens in the workplace" (AIHC Brief, p. 5).

OSHA is gratified that its hope for co-operation and candor in this proceeding was far exceeded by the responsible public response and participation. Indeed, we believe that this entire rulemaking provides justification for the rationale underlying the legal process by which such actions of Federal agencies are finally decided. As the Director of Health Standards Programs stated on the first day of the hearing:

"In its preamble to this proposal, OSHA has attempted to explain in detail the reasons for each provision in the proposal. The scientific debate behind each policy has been described; OSHA's position has been stated as clearly as we were able; other regulatory views have been identified; and opposing arguments summarized. We welcome the impressive array of scientific experts and other parties who will testify on behalf of industry, unions, public interest groups, and the government. Their testimony and statements will help build an extensive public record which the Agency will closely analyze and draw upon in making our decisions on the final cancer policy regulations.

"Although the proposal reflects the Agency's position at the time it was issued, last October, our mind is open. Our desire to have a rulemaking record which reflects the true spectrum of opinion in the scientific community on every significant issue will be served by hearing all of the testimony in this proceeding.

"This hearing has attracted the largest number of participants in OSHA's seven-year rulemaking history. We were not surprised. The scope of issues raised by the proposal cut across almost every conceivable discipline. We welcome the impressive array of scientific and policy experts who will testify and build a record for the Agency to analyze, and we intend that in this proceeding all facets of the proposal will undergo thorough scientific and policy scrutiny.

"In the interest of creating as full a record as possible, OSHA has requested a relatively large number of individuals to participate in this hearing or to provide statements for the record. Many of these individuals are scheduled to present oral testimony in this hearing. In the interest of time, some are not, but their statements will be placed in the record.

"All of the distinguished individuals are appearing as individual scientists or citizens to present their individual views, except in the case of NIOSH or where the witness has indicated otherwise. Because OSHA requested an individual to submit a statement for the record, or testimony for this hearing does not necessarily mean that OSHA subscribes to any or all of the views presented in that statement. Again, for the purposes of developing a full and complete record, OSHA encouraged all of these persons participating at its requests to cover any or all areas of disagreement with the proposal if they so desired. These statements, therefore, as the cover sheet on them indicates, are statements requested by OSHA, not statements from OSHA or statements by OSHA witnesses in the traditional legal sense." (Wrenn, Tr. 21–23)

OSHA believes that the rulemaking proceeding provided OSHA with greater insights into the rational regulation of substances which present potential cancer hazards to humans.

The hearings began on May 16, 1978, before the Department of Labor's

*The term used by FDA in 44 FR 17090 (March 20, 1979).

Administrative Law Judge Jean Greene. In general, hearings were held each working day thereafter and ended on July 25, 1978. The Record was finally closed after various extensions on December 19, 1978. The Record was certified by Judge Greene on January 23, 1979.

OSHA requested 54 experts in the field of carcinogenesis from all relevant disciplines to present written statements. Forty-six of those witnesses were actually presented at the hearing for cross-examination, including the Director of NCI, Arthur C. Upton; the Director of NIEHS, David P. Rall; the Commissioner of FDA, Donald Kennedy; the Chairperson of the CPSC, S. John Byington; and the EPA Assistant Administrator for Toxic Substances, Steven Jellinek. None of these witnesses nor any other persons requested to be witnesses by OSHA left the witness stand until the questioning of such witness by all participants and attorneys in the hearing was complete. All other persons invited by OSHA to file statements as witnesses were available for questioning upon request but no such request was ever made by any participant to this rulemaking. The public filed many witness statements, pre-hearing comments and exhibits in the Record. The transcript, which consists almost solely of responses to questions, is over 8,500 pages. Large volumes of exhibits and references, primarily scientific papers and articles, were submitted for the Record. Over one hundred seventeen post-hearing statements, comments and briefs were received. Eleven other comments were submitted by persons who did not participate in this rulemaking. It is estimated that the total Record consists of over 250,000 pages.

An impressive feature of the hearing record was the high scientific quality of much of the testimony. The list of witnesses as pointed out above included the Directors of NCI and NIEHS. In addition, many distinguished cancer researchers from these institutes, NIOSH, other federal, state and international agencies, the academic community, private research Institutes and industrial research departments also appeared. Many witnesses presented extensive, up-to-date reviews of various aspects of carcinogenesis, including extensive documentation from the scientific literature or their own work. In addition to many volumes of scientific papers and reviews, a number of reports of expert committees of the National Academy of Sciences and other scientific bodies were incorporated into the Record. Several participants pointed out that OSHA's original proposal was documented primarily with references to reviews and committee reports published in the period 1969–76. The extensive documentation submitted for the hearing record has enabled OSHA to update this documentation and to incorporate many primary references reflecting current scientific knowledge.

4. The Interagency Regulatory Liaison Group (IRLG)

Much has been made of the fact that, pursuant to the belief of the President of the United States that federal agencies involved in common areas of endeavor should at least attempt to coordinate their activities, the Administrator of EPA, the Assistant Secretary of Labor for OSHA, the Commissioner of FDA and the Chairperson of CPSC formalized in 1977 a degree of cooperation and coordination between their four regulatory agencies (that had existed for years in varying degrees) known as the Interagency Regulatory Liaison Group or IRLG.

AIHC has claimed that OSHA's participation in the development of an IRLG "Risk Assessment" document has somehow tainted the OSHA cancer policy. OSHA does not agree. First, every decision in this cancer policy is based exclusively upon the Record from the proceeding. Moreover, there is nothing unique about OSHA participating in a number of activities at the same time that cover the same or related issues. Thus, not only did OSHA participate in developing the IRLG risk assessment document, but it also issued standards on several carcinogenic substances including arsenic, benzene and acrylonitrile during the two years since the proposed cancer policy was published. OSHA believes that it would be impossible for it to carry out its statutory responsibilities if it were foreclosed from considering, in other contexts, issues it is considering with regard to a specific regulation.

PART A. THE RATIONALE AND NEED FOR THIS GENERAL POLICY

II. THE REGULATORY DILEMMA

Any decision as to how to regulate carcinogens is obviously complex. Despite some advances in our understanding of cancer, the fundamental causes and mechanisms elude us. Chemical or physical agents known or suspected to pose a risk of inducing cancer in humans present certain problems unique to the regulation of toxic materials in the workplace, which are discussed below. And with the increasing number of environmental chemicals, the number of carcinogens also is likely to increase, together with the size and complexity of OSHA's rulemakings and the concomitant Records and related issues consistently raised in various federal Courts of Appeals.

Perhaps the most eloquent statement of the problems faced by OSHA or any regulatory agency in this area concerning regulation of human exposures to possible carcinogenic substance was made by Dr. Richard Bates (NIEHS, FDA) in his direct testimony concerning the historical example of the Broad Street pump:

"A classic episode in the history of disease prevention took place in London in 1854. An epidemic of cholera occurred in the neighborhood around Broad Street. John Snow, the hero of the story, studied the habits of the victims and found that almost all obtained their water from the well on Broad Street. Swift action was taken; the pump was closed down and the epidemic rapidly subsided. This disease was caused by exposure to the bacterium *Vibrio cholerae.* One can imagine the reaction that might occur today if it were proposed to close down the pump on the basis of evidence of the kind obtained by John Snow. Many scientists would point out that it had not been conclusively demonstrated that the water was the cause of the disease. They would be troubled because of the lack of satisfactory theoretical knowledge to explain how the water could have caused the disease. Furthermore, other habits of those who had become ill had not been adequately investigated, so it would not be possible to rule out other causes of the disease. The scientists would have been correct. Others would have pointed out that some members of the community who drank from the Broad Street well had not succumbed to cholera. Thus, even if there were something wrong with the water, there must be other factors involved, and if we could control these we would not have to be concerned about the water. These conclusions are also correct. Some who consumed water from the Broad Street well would have objected to closing it because the taste of water from other wells was not as agreeable. Finally, if the pump had been owned by an individual who sold the water, he would certainly have protested against closing down his business on the basis of inconclusive evidence of hazard.

"This story illustrates a number of points that need to be kept in mind as we examine the proposed carcinogen policy of the Occupational Safety and Health Administration. First, if human disease and deaths are to be prevented, it is often necessary to control exposure for which there is some evidence of hazard before that evidence has reached the point that scientists would universally regard as conclusive. The alternative, to continue exposure until there is conclusive evidence of human hazard, is a form of human experimentation that our society finds increasingly unacceptable.

"Second, development of a disease in any individual is the result of complex interactions of a variety of factors including his or her genetic susceptibility; environmental influences on the person's state of susceptibility that may include such things as exposure to other harmful agents in the environment, the person's state of nutrition, age and general health; and finally the level and extent of exposure to specific disease causing agents. These principles hold true for cholera; not all who drank from the Broad Street well developed cholera. These principles also apply to cancer induction; cancer develops in susceptible individuals exposed to carcinogenic agents.

"Third, the incidence of disease in a population can be reduced either by reducing exposure to specific causative agents or through general or specific measures that reduce the level of susceptibility of the population to the causative agents. The state of our knowledge about the specific disease determines which measures can be applied most successfully at any particular time in history. During John Snow's time, removing the supply of contaminated water was the most feasible approach. Today, cholera can also be controlled through immunization and mortality can be reduced through specific therapy. During John Snow's time, however, the latter options were not available. Control of tuberculosis has resulted as much from better nutrition and improved living conditions as it resulting from hospitalization of diseased individuals. These general health measures increased resistance of the population to the disease agent. More specific immunization techniques against tuberculosis have been developed, but their effectiveness has been a matter of considerable debate for many years.

With cancer, the major method of prevention available to us today is to prevent exposure to chemicals and radiations capable of inducing the disease." (Bates, S. 1–4; footnotes omitted.) (Elaborated in Bates, Preventing Occupational Cancer, 28 Environmental Health Perspectives [NIEHS] pp. 303–310 [1979]).

In addition, Dr. Bates had earlier observed:

"Occupational carcinogenesis is the result of failure to detect carcinogens in the laboratory before there is exposure of human populations, and in some cases, failure to take adequate, protective measures even after a carcinogenic risk has been identified." Bates, "Laboratory Approaches to the Identification of Carcinogens," in Occupational Carcinogenesis, Vol. 271 of the Annals of the New York Academy of Sciences (1976).

The Assistant Secretary of Labor and the Secretary of Labor emphatically agree with Dr. Bates. The primary purpose of the Act is to assure, so far as possible, safe and healthful working conditions for every American employee over the period of his or her working lifetime. One means prescribed by Congress to achieve this goal is the mandate given to, and the concomitant authority vested in, the Secretary of Labor to set mandatory safety and health standards. The Congress specifically mandated that:

"The Secretary, in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life. Development of standards under this subsection shall be based upon research, demonstrations, experiments, and such other information as may be appropriate. In addition to the attainment of the highest degree of health and safety protection for the employee, other considerations shall be the latest available scientific data in the field, the feasibility of standards, and experience gained under this and other health and safety laws." (Section 6(b)(5)).

In setting standards pursuant to the Act, the Secretary is also expressly required to consider the feasibility of the proposed standards. Senate Committee on Labor and Public Welfare, S. Rep. No. 91–1282, 91st Cong., 2d Sess., p. 58 (1970). Nevertheless, considerations of technological feasibility are not limited to devices already developed and in use. Standards may require improvements in existing technologies or require the development of new technology. *The Society of the Plastics Industry* v. *OSHA, supra* at 1390. In practice, OSHA also takes into account economic considerations in determining what is feasible.

Where appropriate, the standards are required to include provisions for labels or other forms of warning to apprise employees of hazards, suitable protective equipment, control procedures, monitoring and measuring of employee exposure, employee access to the results of monitoring, appropriate medical examinations and training and education. Moreover, where a standard prescribes medical examinations or other tests, they must be available at no cost to the employees (section 6(b)(7)). Standards may also prescribe recordkeeping requirements where necessary or appropriate for enforcement of the Act or for developing information regarding occupational accidents and illnesses (section 8(c)).

Sections 2(b)(5), 2(b)(6), 6, 20, 21, 22, and 24 of the Act reflect the Congress's recognition that conclusive medical or scientific evidence, including causative factors, epidemiological studies or dose response data may not exist for many toxic materials or harmful physical agents. Nevertheless, the Congress mandated that standards should not be postponed because definitive medical or scientific evidence is not currently available. Indeed, while final standards are based on the best available evidence, the legislative history makes it clear that the Congress was aware of the "frightening gap" between "our knowledge about [toxic] substances, and what we need to know" (Leg. Hist. 1044–1045). The best available evidence provision was inserted because "it is not intended that the Secretary be paralyzed by debate surrounding diverse medical opinion." House Comm. On Education and Labor, H.R. Rep. No. 91–1291, 91st Cong., 2d Sess. 18 (1970). In fact, foremost among the concerns of the Congress in enacting OSHA was the ever-increasing number of toxic materials and harmful physical agents in the workplace. Leg. Hist. 142–143, 159–160, 411–415, 503, 510, 845–846, 1061. The Senate Committee on Labor and Public Welfare, for example, reported that toxic agents were a pernicious threat to employee health:

"Workers in the dusty trades still contract various respiratory diseases. * * * Carcinogenic chemicals, lasers, ultrasonic [sic] energy, beryllium metal, epoxy resins, pesticides, among others, all present incipient threats to the health of workers. * * * It is estimated that every 20 minutes a new and potentially toxic chemical is introduced into industry. New processes and new sources of energy present occupational health problems of unprecedented complexity.

"Recent scientific knowledge points to hitherto unsuspected cause-and-effect relationships between occupational exposures and many of the then so-called chronic diseases—cancer, respiratory ailments, allergies, heart disease, and others. In some instances, the relationship appears to be direct: asbestos, ionizing radiation, chromates, and certain dye intermediaries, and among others, are directly involved in the genesis of cancer. In other cases, occupational exposures are implicated as contributory factors. The distinction between occupational and nonoccupational illnesses is growing increasingly difficult to define."

Id. at 142.*

Death from such "silent killers"** was occurring because many employers had little economic incentive to provide healthful workplaces. "[M]any employers—particularly smaller ones—simply cannot make the necessary investment in health and safety, and survive competitively, unless all are compelled to do so." Id. at 144 (Senate Report). Because employees often moved from job to job, "an employer investing in current occupational health precautions would receive no future benefits, not even in the reduction of workmen's compensation costs. He

*The House Committee on Education and Labor likewise identified exposure to toxic substances as a principal concern. *Id.* at 844–846.

**Leg. Hist. 1044–45 (Rep. Udall).

might be paying for the past neglect of another employer." Id. at 854 (House Report).

In the circumstances, the Congress concluded, the best approach was to impose a duty on all employers to provide workplaces as free from health hazards as possible. Congress recognized that achievement of this goal would require substantial investment in health protection (Leg. Hist. 444, 510, 525–526, 1004, 1030, 1040, 1150–1151), and that these costs "would be put into consumer goods . . ." *Id.* at 444 (Sen. Yarborough).*** But the Congress concluded that the expense of providing a safe and healthful place to workers is a necessary and reasonable cost of doing business. Senator Eagleton of Missouri observed that "[t]he costs that will be incurred by employers in meeting the standards of health and safety to be established under this bill are, in my view, reasonable and necessary costs of doing business. Whether we, as individuals, are motivated by simple humanity or by simple economics, we can no longer permit profits to be dependent upon an unsafe or unhealthy worksite." *Id.* at 1150–1151. Senator Williams of New Jersey, one of the principal authors of the Act, stated that the costs of compliance was "the price we should pay for the 80 million workers in America." *Id.* at 444.****

This congressional judgment has been supported by the Courts which have reviewed standards promulgated under the Act. In *Industrial Union Department, AFL–CIO* v. *Hodgson,* 499 F. 2d 467 (D.C. Cir. 1974), the United States Court of Appeals considered the Secretary of Labor's delegated mandate and power under the Act to protect the health of workers from exposure to asbestos. It stated (499 F. 2d at 474):

"From extensive and often conflicting evidence, the Secretary in this case made numerous factual determinations. With respect to some of those questions, the evidence was such that the task consisted primarily of evaluating the data and drawing conclusions from it. The court can review substantial support for the Secretary's findings. But some of the questions involved in the promulgation of these Standards are on the frontiers of scientific knowledge, and consequently as to them insufficient data is presently available to make a fully informed factual determination. Decision making must in that circumstance depend to a greater extent upon policy judgments and less upon purely factual analysis.[18]"

"[18] Where existing methodology or research in a new area of regulations is deficient, the agency necessarily enjoys broad discretion to attempt to formulate a solution to the best of its ability on the basis of available information, Permian Basin Area Rate Cases, 390 US 747, 811, 88 S. Ct. 1344, 20 L. Ed. 2d 312 (1968)."

This rationale was likewise applied in *The Society of the Plastics Industry, Inc.* v. *OSHA* 509 F.2d 1301 (2d Cir.), *cert. den. sub nom. Firestone Plastics Co. v. U.S. Dep't of Labor* 421 U.S. 992 (1975), where the Second Circuit reviewed regulations limiting worker exposure to vinyl chloride. The Court stated at 1380:

"As in *Industrial Union Department, AFL–CIO v. Hodgson, supra,* the ultimate facts here in dispute are on the frontiers of scientific knowledge, and, though the factual finger points, it does not conclude. Under the command of OSHA, it remains the duty of the Secretary to act to protect the workingman, and to act even in circumstances where existing methodology or research is deficient. The Secretary, in extrapolating the MCA study's findings from mouse to man, has chosen to reduce the permissible level to the lowest detectable one. We find no error in this respect."

And in *Ethyl Corp.* v. *EPA* 541 F.2d 1 (D.C. Cir. 1976), the Court of Appeals affirmed the EPA Administrator's decision to limit lead in gasoline, based in large part upon the rationale of *IUD* v. *Hodgson, supra* and *SOCMA* v. *OSHA, supra.* The Court stated at pp. 24–28:

"Questions involving the environment are particularly prone to uncertainty. Technological man has altered his world in ways never before experienced or anticipated. The health effects of such alterations are often unknown, sometimes unknowable. While a concerned Congress has passed legislation providing for protection of the public health against gross environmental modifications, the regulators entrusted have not been endowed with a prescience that removes all doubt from their decision-making. Rather, speculation, conflicts in evidence, and theoretical extrapolation typify their every action. How else can they act, given a mandate to protect the public health but only a slight or nonexistent data base upon which to draw? Never before have massive quantities of asbestiform tailings been spewed into the water we drink. Never before have our industrial workers been occupationally exposed to vinyl chloride or to asbestos dust. Never before have hundreds of thousands of tons of lead emissions been disgorged annually into the air we breathe. Sometimes, of course, relatively certain proof of danger or harm from such modifications can be readily found. But, more commonly, 'reasonable medical concerns' and theory long precede certainty. Yet the statutes—and common sense—demand regulatory action to prevent harm, even if the regulator is less than certain that harm is otherwise inevitable.

"Undoubtedly, certainty is the scientific ideal—to the extent that even science can be certain of its truth. But certainty in the complexities of environmental medicine may be achievable only after the fact, when scientists have the leisurely and isolated scrutiny of an entire mechanism. Awaiting certainty will often allow for only reactive, not preventive, regulation. Petitioners suggest that anything less than certainty, that any speculation, is irresponsible. But when statutes seek to avoid environmental catastrophe, can preventive, albeit uncertain, decisions legitimately be so labeled?" 541 F.2d 1 at pp. 24–25, omitting footnotes.

"That petitioners, and their scientists, find a basis to disagree is hardly surprising, since the results are still uncertain, and will be for some time. But if the statute accords the regulator flexibility to assess risks and make essentially legislative policy judgments, as we believe it does, preventive regulation based on conflicting and inconclusive evidence may be sustained. Recent cases have recognized this flexibility in similar situations [citing *IUD* v. *Hodgson; SOCMA* v. *OSHA, supra;* and *Reserve Mining Co.* v. *EPA* 514 F. 2d 492 (8th Cir. 1975) (en banc), 541 F. 2d 1 at 27.

* * * * *

"Where a statute is precautionary in nature,[57] the evidence difficult to come by, uncertain, or conflicting because it is on the frontiers of scientific knowledge, the regulations designed to protect the public health, and the decision that of an expert administrator, we will not demand vigorous step-by-step proof of cause and effect. Such proof may be impossible to obtain if the precautionary purpose of the statute is to be served." 541 F. 2d 1 at 28.

"[57] "Or, as with OSHA, mandatory in its command to act. *See* Note 56 *supra.*"

In *Certified Color Manufacturers Ass'n* v. *Mathews,* 543 F.2d 284 (D.C. Cir. 1976), the Commissioner of FDA had terminated provisional approval of the color additive "Red Dye No. 2" because of suggestive evidence that it caused cancer in rats. In affirming that action, the Court stated at 297–298:

"Courts have traditionally recognized a special judicial interest in protecting the public health, particularly where 'the matter involved is as sensitive and frightladen as cancer'. Where the harm envisioned is cancer, courts have recognized the need for action based upon lower proof than otherwise applicable." (footnotes omitted).

And finally, in *EDF* v. *EPA (PCBs),* 598 F.2d 62 (D.C. Cir. 1978) the Court said at 88:

"After review of the authorities on the difficult issue of carcinogenic effect, we conclude that EPA's evidence furnishes adequate support for its prohibition. An

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***Senator Yarborough, a co-sponsor of the bill that was ultimately enacted, replied to the claim that the bill would be expensive (id. at 510):

"One may well ask too expensive for whom? * * * Is it too expensive for the employee who loses his hand or leg or eyesight? Is it too expensive for the widow trying to raise her children on meager allowance under the workmen's compensation and social security? * * *

"We are talking about people's lives, not the indifference of some cost accountants. We are talking about assuring the men and women who work in our plants and factories that they will go home after a day's work with their bodies intact."

****Congress anticipated that to some extent the cost of compliance would be recovered in savings in health care, workmen's compensation, lost wages and lost productivity. Id. at 142, 844–845, 1001.

administrator has a "heavy burden" to "explain the basis for his decision to permit the continued use of a chemical known to produce cancer in experimental animals." *EDF* v. *Ruckelshaus* (DDT), 439 F.2d 584, 596 n.41 (D.C. Cir. 1971); *accord, EDF* v. *EPA* (heptachlor and chlordane), 584 F.2d 998, 1005 (D.C. Cir. 1978), *cert. denied,* 431 U.S. 925 (1977); *EDF* v. *EPA* (aldrin and dieldrin), 510 F.2d at 1302; *see EDF* v. *Department of Health, Education and Welfare,* 428 F.2d at 1090–92. When firm evidence establishes that a chemical is a carcinogen, statutes generally leave an administrator no alternative but to step in to protect the public.

"On the other hand, when the evidence is less than firm, but merely suggests that a chemical may be a carcinogen, the same "heavy burden" may not attend administrative inaction. The decision to act in such a case has been held to fall within the discretion of the Administrator. For example, in *Reserve Mining Co.* v. *EPA,* 514 F.2d 492 (8th Cir. 1975) (en banc), EPA sought to abate discharge of mining refuse into Lake Superior "under an acceptable but unproved medical theory," that the discharges were carcinogenic. 514 F.2d at 529. The court concluded that the discharges should be abated, even though there would be a heavy cost, including possible loss of many jobs, to the local economy. Id. at 514–20, 535–40. Similarly, in *Certified Color Manufacturers Association* v. *Mathews,* 543 F.2d 284 (D.C. Cir. 1976), the Food and Drug Administration (FDA) terminated its provisional approval of a color additive used to dye food on the basis of a vigorously debated study of the additive's carcinogenic effects. This court concluded that the FDA action should be upheld, based upon FDA's scientific judgment that the study was not conclusive, but was merely suggestive of carcinogenicity. Id. at 297. "Courts have traditionally recognized a special judicial interest in protecting the public health, particularly where "the matter involved is as sensitive and fright-laden as cancer." Where the harm envisaged is cancer, courts have recognized the need for action based upon lower standards of proof than otherwise applicable." Id. at 297–98 (footnotes omitted) quoting *EDF* v. *EPA* (DDT), 465 F.2d 528, 538 (D.C. Cir. 1972). The courts have frequently upheld regulations based on evidence of carcinogenic effects. See, e.g., *American Iron & Steel Institute* v. *OSHA,* No. 76–2358, slip op. at 31–32 (3d Cir. March 28, 1978) (coke oven emissions); *Society of the Plastics Industry* v. *OSHA,* 509 F.2d at 1311 (vinyl chloride); *Synthetic Organic Chemical Manufacturers Association* v. *Brennan,* 503 F.2d 115, 1159–60 (3d Cir.) (same), *cert. denied,* 420 U.S. 973 (1974).

"These cases demonstrate that inevitable tension attending regulation of carcinogens. Frequently, such regulations have severe economic impact. ~~Indeed,~~ sometimes, as alleged by industry petitioners in this case, such regulations may jeopardize plants or whole industries, and the jobs depending on them. In such circumstances, the temptation to demand that the agency furnish conclusive proof of carcinogenicity as support for the regulations is great. However, the decision to delegate authority to an agency to control suspected carcinogens is a legislative judgment that is not open to question in this court. Congress's direction to EPA to protect against incompletely understood dangers could not be carried out if we were to adopt the proof requirements advocated by industry petitioners."

This proposal marks a departure from OSHA's usual pattern of a substance-by-substance approach in setting health standards concerning exposures to potential occupational carcinogens. For the reasons set forth herein, OSHA believes that such an approach is not only proper and necessary but in fact compelling because of its "experience gained under this and other health and safety laws". (The Act, section 6(b)(5).) Moreover, OSHA believes that by establishing a rational and predictable policy concerning the regulation of exposures to occupational carcinogens, employers, employees, the general public, the scientific community and public interest groups will not only benefit from improved employee health, but also experience greater efficiencies in their own activities.*

Employees are exposed to many substances on a daily basis. Obviously, most of these substances are not carcinogenic. Yet, some may be. OSHA believes that this general policy and procedure will facilitate the sifting through the evidence concerning substances which may be imputed to be potential carcinogens and the application of uniform, predictable criteria in order to assess whether such substances should indeed be treated as carcinogenic. Without such a system and appropriate criteria, OSHA believes that this task cannot be accomplished in a timely and efficient manner. With an appropriate system and criteria, worker health will be protected efficiently without rediscussing or relitigating, time and time again, the same issues and without unnecessarily draining limited industry, union, public interest, scientific and government resources. As a result of this policy, OSHA believes that these limited resources will focus on the most substantial issues in OSHA rulemaking proceedings, thus leading to more compact and useful Records in a shorter period of time. In addition, this policy will result in continuity of approach, even in the face of changes of policymakers. This new approach is intended to ameliorate certain administrative problems in standard setting. One significant aspect of past rulemakings concerning carcinogens was the enormous time period between OSHA's initial **Federal Register** notices and final judicial actions. For example, in its nine (9) year history, OSHA has concluded only seven (7) rulemaking proceedings in regulating carcinogens. Moreover, it should be noted that the total time the official process took from the date of the first official announcement in the **Federal Register** to completion of the judicial review of the final standard does not necessarily include the time required to analyze the facts and develop the proposal in the first instance, which itself can be considerable.** Finally, it should be noted that the procedures followed in each of the following cases differed because of an attempt to speed up the process. None of the differing procedures succeeded in achieving that goal.

a. Asbestos

An emergency temporary standard regulating occupational exposures to asbestos was published on December 7, 1971 (36 FR 23207) and not judicially contested; a permanent standard was proposed on January 12, 1972 (37 FR 466) and, after a short hearing, was published in final form on June 7, 1972 (37 FR 11318); the permanent standard was contested in *Industrial Union Department, AFL–CIO* v. *Hodgson* on July 27, 1972, and affirmed in 499 F.2d

*While OSHA will not elaborate upon the lengthy time consuming "case-by-case" rulemakings experienced by other agencies under other statutes, an excellent discussion of the same problems appears in McGarity, "Substantive and Procedural Discretion in Administrative Resolution of Science Policy Questions: Regulating Carcinogens in EPA and OSHA". 67 Georgetown Law Journal 724 (~~February 1979~~). ~~Also see~~ Berger and Riskin, Economic and Technological Feasibility in Regulating Toxic Substances Under the Occupational Safety and Health Act, 7 Ecology Law Quarterly 285 (1978). The scientific commentators have also recommended a generic, rather than a case-by-case approach, to regulating carcinogens for the same reasons. See National Academy of Sciences—National Research Council, Decisionmaking for Regulating Chemicals in the Environment 33 (1975).

**Only two other health standards have been promulgated during the history of OSHA namely: standards regulating occupational exposures to inorganic lead and cotton dust. In the case of the standard regulating occupational exposure to lead, the proposed final standard was published on October 3, 1975 (40 FR 45934), extensive hearings held and the final standard published on November 14, 1978, a process that took over 36 months. An appeal is pending in the Court of Appeals for the District of Columbia in *Lead Industries, Inc.* v. *OSHA.* In the case of the standard regulating occupational exposure to cotton dust, an advance notice of proposed rulemaking was published on December 27, 1974 (39 FR 44769), a proposed permanent standard published on December 28, 1976 (41 FR 54498), extensive hearings held in April and May of 1977, and final standards published as to Cotton Dust and Cotton Dust in Cotton Gins on June 23, 1978 (43 FR 27350 and 27418), a process that took over 42 months. Appeals were recently decided by the Court of Appeals for the District of Columbia in *AFL–CIO* v. *Marshall* and *Texas Independent Ginners Assoc.* v. *Marshall.*

467 on April 17, 1974, the entire process consuming about 29 months.*

b. Fourteen Carcinogens

On July 6, 1972, OSHA requested information concerning fifteen substances (37 FR 13285). A package of fourteen (14) emergency temporary standards regulating occupational exposures to a like number of carcinogens was published on May 3, 1973 (38 FR 10929), contested in part in *Dry Color Manufacturers' Assn.* v. *Brennan* and vacated on October 4, 1973 by the Third Circuit Court of Appeals at 486 F.2d 98; an advisory committee was appointed and began its meetings on June 25, 1973, the proposed permanent standard was published on July 16, 1973 (38 FR 18800) and amended on August 16, 1973 (38 FR 22141), a hearing was held in September 1973 and the final standard published on January 29, 1974 (39 FR 3756), contested in *Synthetic Organic Chemical Manufacturers Assn. (SOCMA)* v. *Brennan* I (EI) on January 29, 1974 and *SOCMA* v. *Brennan* II (MOCA) on February 4, 1975. In *SOCMA* v. *Brennan* I, the Third Circuit affirmed in part in 503 F.2d 1155 on August 26, 1974, *cert. den.* on March 17, 1975 in 420 U.S. 973. A petition for rehearing was denied on October 6, 1975. In *SOCMA* v. *Brennan* II, the Third Circuit affirmed in 506 F.2d 385 on December 17, 1974. A petition for certiorari was filed on March 20, 1975 and denied by the Supreme Court on October 6, 1975 *sub nom. Oil, Chemical and Atomic Workers* v. *Dunlop* in 423 U.S. 830. The entire process consumed about 40 months.

c. Vinyl chloride

A fact-finding hearing concerning vinyl chloride was announced on January 30, 1974 (39 FR 3874) and held on February 15, 1974. An emergency temporary standard regulating occupational exposure to vinyl chloride was published on April 5, 1974 (39 FR 12341) and not judicially contested, a proposed permanent standard was published on May 10, 1974 (39 FR 16896), the permanent standard published on October 4, 1974, (39 FR 35892), contested in *The Society of the Plastics Industry* v. *OSHA* on October 1, 1974, and affirmed in 509 F.2d 1301 on January 21, 1975, *cert. den. sub nom. Firestone Plastics Co.* v. *U.S. Department of Labor* in 421 U.S. 992, on May 27, 1975, the entire process consuming 15 months.

d. Coke oven emissions

An advisory committee concerning occupational exposures to coke oven emissions was appointed on August 12, 1974, and held twenty-eight days of meetings during which testimony was presented by numerous experts and parties and over 200 exhibits received, the proposed permanent standard was published on July 24, 1975 (40 FR 40849), promulgated on October 22, 1976 (41 FR 46742), contested in *American Iron and Steel Institute* v. *OSHA* on October 23, 1976, and affirmed in 577 F.2d 825 on March 28, 1978, petition for *certiorari pending* in the United States Supreme Court, the entire process consuming 66 months so far.

e. Arsenic

An advance notice of proposed rulemaking concerning occupational exposures to inorganic arsenic was published on June 11, 1974 (39 FR 20494), a fact-finding hearing was announced on August 30, 1974 (39 FR 31644), held on September 20, 1974, a proposed standard was published on January 21, 1975 (40 FR 3392), a final permanent standard published on May 5, 1978 (43 FR 19584), contested in *ASARCO* v. *OSHA* on May 5, 1978 and judicial review is pending in the Ninth Circuit Court of Appeals and decision has been deferred pending the result of the Supreme Court decision in the case of the contested standard regulating occupational exposures to benzene, *infra.* The entire ongoing process has therefore consumed 67 months.

f. Benzene

An emergency temporary standard regulating occupational exposures to benzene was published on May 3, 1977 (42 FR 22516), stayed in *API* v. *OSHA* by the Fifth Circuit Court of Appeals on May 20, 1977, a proposed permanent standard was published on May 27, 1977 (42 FR 27482), published in final form on February 10, 1978 (43 FR 5918), contested in *American Petroleum Institute* v. *OSHA* on February 2, 1978, and vacated in 581 F.2d 493 on October 5, 1978, *certiorari granted* in *Marshall* v. *API* 440 U.S. 906 on February 21, 1979 by the United States Supreme Court, the entire process, so far, consuming 31 months.

g. Acrylonitrile

On June 29, 1977 (42 FR 33043), and July 5, 1977 (42 FR 34326), OSHA requested public comments concerning occupational exposure to vinyl cyanide or acrylonitrile. An emergency temporary standard regulating occupational exposures was published on January 17, 1978 (43 FR 2586), contested on January 17, 1978, the stay was denied in *Vistiron* v. *OSHA* on March 28, 1978 in the Sixth Circuit, a permanent standard was proposed on January 17, 1978, (43 FR 45762), hearings held in March and April 1978 and the final standard issued on October 3, 1978 (43 FR 45762). That final standard was not judicially contested, although the entire process consumed 16 months even after the Manufacturing Chemists Association and Dow Chemical Co. on the one hand and E. I. du Pont de Nemours & Co. Inc. on the other hand informed OSHA that such substance was a potential carcinogen based on both animal and human evidence in March and May of 1977 respectively.

h. Beryllium

In the case of a standard regulating occupational exposures to beryllium, the proposed standard was published on October 17, 1975 (40 FR 4814). Hearings were held during August and September 1977. A final standard is pending with the process to date having consumed at least 51 months.

In sum, OSHA believes that the length of time consumed in official regulatory and judicial processes will be shortened after the promulgation of this Part for the following reasons: the periodic announcement of regulatory priorities and advance notice of identification and classification criteria will enable all participants in the regulatory process, including OSHA staff, to act with greater efficiency and certainty in framing the truly critical issues in any rulemaking and locating the required technical and scientific expertise early in the proceeding. This should shorten and sharpen the rulemakings. Also the reviewing courts will be presented with rulemaking records of improved coherence, relevance and reduced size, aiding their deliberations.

Other administrative problems faced by OSHA in promulgating regulations in this area on a case-by-case basis are expected to be mitigated by these regulations. OSHA had stated that the present system unreasonably takes the time of scientific experts who were asked to present statements concerning identical issues in various proceedings. For example, Dr. Rall (Director, NIEHS) testified:

". . . I think the discussion of the issues can and should continue forever.

Mr. Hanson [of Dow Chemical Co.] Which forum, sir?

* * * * *

Dr. Rall: In scientific forums. Sometimes the regulatory agency has to say—and I think it is perfectly proper—that we accept the current state of knowledge and regulate on the basis of it. The point really is that the

*The cancer-causing properties of asbestos were not used as a basis for the 1972 OSHA asbestos standard.

evidence is overwhelming that compounds which are carcinogenic in laboratory animals—and this may well be only in one species in a good test—have a very high probability of being carcinogenic for man.

Mr. Hanson: Sir, if the statement were the only issue being foreclosed in this rulemaking, I am not sure I would have a concern.

* * * * *

Dr. Rall: Well, you know, there are a lot of other issues that I could continue with.

* * * * *

Mr. Hanson: OK. Another foundation, supposedly, is this business of witnesses not wanting or being unable to appear in rulemakings. Do you feel uncomfortable appearing here today talking with me?

Dr. Rall: I do not feel uncomfortable, but I should point out that this entire process is taking a significant amount of my time.

* * * * *

And I am delighted to do it once, but I would simply be unable to do it on a recurring basis, or I could not fulfill the main part of my job, which is to run a research institute.

Mr. Hanson: Yes, Sir.

Dr. Rall: And I think that is a very real consideration.

Mr. Hanson: Yes, indeed, it is, sir. . . .

But would you not, as Director of NIEHS in Research Triangle Park want the opportunity in an OSHA rulemaking proceeding to come back and talk with me about something new, exciting or revolutionary in the field of carcinogenesis?

Dr. Rall: Absolutely. And if and when that occurs, I would urge OSHA to promulgate [an] amended or a new standard.

* * * * *

But I have no assurance that that is going to occur six months from now or sixteen years from now, . . .". (Rall, Tr. 406–09)

In addition, the present system hardly guarantees a continuity of approach in every case, whether it be within the Agency or within the Courts. And finally, the manpower resources of the Department of Labor are simply overwhelmed using the present approach.

In short, OSHA believes that administrative feasibility supports such a procedure as is provided for in this document. The necessity to resolve basic scientific policy issues anew, in each rulemaking, has increased the burden on the Department of Labor and members of the scientific community called upon to address these widely accepted policies. Moreover, relitigation of these issues in the Federal courts has also drained staff time and energy and has inhibited OSHA initiatives while its policy determinations were repeatedly relitigated.

OSHA also notes that the legal and administrative resources of all parties are similarly taxed by these repeated assaults on widely accepted policy positions taken by Federal regulatory agencies regulating potential carcinogens. Thus, unions, environmental groups, consumer federations, trade associations, and large and small employers, have dedicated often limited time, effort and money to opposing fruitlessly, or supporting superfluously, rulemakings, results of which are usually determinations which have been resolved consistently in the past. OSHA believes these efforts by all these parties may have detracted from more meaningful actions to protect employees, such as increased research to identify hazards and to improve the efficiency and cost-effectiveness of control technology and methods, and the education and training of employees.

It is OSHA's belief that if these regulations are not promulgated, with the present resources the output of standards to protect American workers from potential carcinogenic substances may never be adequate. Indeed, to follow the past system and procedure for each and every individual substance and hazard would be, we believe, beyond the abilities of any agency, no matter how large a staff it may have.

The vinyl chloride standard (29 CFR 1910.1017) provides a striking example of the effort which has been required for standard promulgation, under optimum circumstances, pursuant to the *de novo* case-by-case approach. That standard, developed on a top priority basis with resources borrowed from other on-going projects, took the full statutory six months from the issuance of the emergency temporary standard, through the required hearings and the adequate review of the record, to publish a final rule. And that time does not include the time and resources devoted to the earlier fact-finding hearing and the necessary preparation of the emergency temporary standard and preamble themselves. Moreover, that time does not include the resources that were required to defend the final standard in the appellate courts. The ETS itself was not contested.

The vinyl chloride rulemaking proceedings concerned a substance which undisputedly was a human carcinogen. Yet, controversy raged during the hearing concerning the precise level of exposure which posed a hazard, whether a "safe" exposure level existed, whether animal data could be prudently extrapolated to man in quantitative terms and the appropriateness of the regulatory requirements. The comments and testimony concerning these issues were discussed in a significant part of the more than 600 written comments, 200 written and oral hearing submissions, the hearings, and the 4,000 page record.

Notwithstanding the bulk and comprehensiveness of the record, OSHA finally determined that the record did not provide definitive answers to these questions. The Agency declared, "(w)e cannot wait until indisputable answers to these questions are available, because lives of employees are at stake" (39 FR 35892).

OSHA, therefore, like other administrative agencies in the past, has determined that it is necessary at this time, in the fulfillment of its statutory objectives, to reshape the size and content of its rulemaking proceedings at least insofar as potential carcinogens are concerned. This set of regulations finalized today incorporates policy determinations concerning how and when chemical or physical substances should be identified, classified, and consequently regulated, as posing a carcinogenic risk to humans.

It is OSHA's intention to limit the issues in the subsequent 6(b) rulemakings on individual substances, to topics and issues specific to those individual substances. The rehearing of the validity of this classification system and most of the other general policy determinations as described in this document, including the procedural structure intended to be followed, are not to be the subject of those individual rulemakings. However, other than the foreclosed policy determination that employees shall be exposed to Category I potential carcinogens at the lowest level feasible and that the level should be reached primarily through the use of engineering and work practice controls, hardly any scientific or policy issue is really foreclosed from discussion if certain minimum threshold criteria are met in the subsequent rulemakings. A description is more fully set out below.

The Agency believes that this "generic" form of standard setting will not in any way deny "due process", the statutory procedural requirements set forth in section 6(b) of the Act or in 5 U.S.C. 553, *et seq.*, since every opportunity for notice, comment, and public participation in extensive hearings pursuant to those provisions has been afforded. Moreover, the model regulatory standards we believe are flexible. As pointed out below, with certain limited exceptions, the model standards contain provisions that are no more than guidelines for OSHA and the public in conducting future regulatory activity and are not meant, as was perceived by some of the participants in this rulemaking, to be rigid, to involve irrebuttable presumptions or to provide

the prescribed protection in the most costly manner conceivable. The opposite is our intent. In this document, therefore, OSHA has adopted in large part the proposed language and suggestions of the American Petroleum Institute (API) and others to express more clearly the function of these model standards. The model standards, as did API's model standard: "retain the *types* of requirements contained in the OSHA Proposal, but restructure each provision in the form of guidelines and criteria to permit OSHA and the public to tailor each standard to the specific substances being regulated" (API, Post Hearing Comments, September 15, 1978, p. 16.) And, as promulgated herein, even the provisions in the model standards concerning the "types" of requirements are only presumptive which means that they can be changed, added to or deleted from, as to any given substance, depending upon only a requirement that the proponent of such change satisfactorily explains the basis for such a change from OSHA's general policy concerning regulation of potential occupational carcinogens. The presumption that the types of requirements are to be mandated is *not*, therefore, irrebuttable. Only the decisions that levels of exposure be as "low as feasible" and achieved by way of any practicable combination of "engineering controls and work practices" for Category I toxic substances are presented in this regulation and foreclosed from further discussion in subsequent rulemakings on individual substances. These decisions have been policy determinations made by OSHA in the past in standards issued concerning regulation of exposures to carcinogens and are merely codified by this document.

OSHA has legal authority pursuant to the Act to follow the generic approach to rulemaking. Sections 6(b), 3(8), 2(b)(3) & (9) and 8(g)(2) provide for the promulgation of occupational health standards and this includes methods reasonably necessary and appropriate for such standards and regulations the Secretary deems necessary to carry out his responsibilities. The Secretary believes that the generic approach to rulemaking, establishing general policies in this proceeding and specific requirements in subsequent individual rulemakings is a necessary and reasonable approach to regulating occupational carcinogens in view of the large number of such substances which must be considered and regulated and the weaknesses of the past substance-by-substance approach.

It is well established that administrative agencies have broad discretion in tailoring administrative procedures in informal rulemakings to the needs of efficient regulatory actions so long as the public can effectively present its views and questions the agency's position. The courts have also encouraged agencies to promulgate general rules to guide their decisions in individual cases. *Vermont Yankee* v. *NRDC*, 435 U.S. 519, 545–46 (1978); *SEC* v. *Chenery Corp.*, 332 U.S. 194(1947); *NLRB* v. *Wyman-Gordan* 395 U.S. 759 (1969). They have also generally accepted that particular rulemaking proceedings are within broad grants of statutory authority. *Mourning* v. *Family Public*, 411 U.S. 356 (1972).

In addition to the statutory authority that OSHA has to engage in generic or policy rulemaking. It has long been recognized by the courts that regulatory agencies, such as OSHA, may use innovative rulemaking procedures to set policy, in order to comply with their statutory mandates, even at the expense of nominally depriving interested parties of a hearing on individual claims which may be contrary to the generally announced policy. Thus in 1956, the Supreme Court held that the Federal Communications Commission was not required to give a license applicant a statutorily required hearing, when the applicant did not qualify under the Commission's policy, adopted through rulemaking, that no person could own more than five (5) broadcasting stations. (*United States* v. *Storer Broadcasting Co.*, 351 U.S. 192, 202 (1956). *See also, FPC* v. *Texaco*, 377 U.S. 33 (1964); *Airline Pilots Asso.* v. *Quesada*, 276 F.2d (2nd Cir. 1960). *See also, EDF* v. *EPA* (PCBs) 598 F.2d 62 (D.C. Cir., 1978). In *Texaco* the Supreme Court stated,

"To require the Commission to proceed only on a case by case basis would require it, so long as its policy outlawed indefinite price changing provisions, to repeat in hearing after hearing its conclusions that condemn all of them. There would be a vast proliferation of hearings. . . We see no reason why under the statutory scheme the process of regulation need be so prolonged and so crippled." (p. 112)

The overriding concern in these cases is whether parties had unreasonably been deprived of due process or statutory procedural rights which were intended to assure that the agency would not act arbitrarily in denying claims. OSHA believes that no such deprivation will occur as the result of promulgation of these regulations. We believe that the recent opinion of the Court of Appeals for the District of Columbia in *EDF* v. *EPA* (PCBs) 598 F.2d 62 (1978) is apposite. There the Court stated:

Finally, in reviewing EPA's policy of regulating less chlorinated PCBs in part on the basis of what is known about more chlorinated PCBs, we must recognize considerations of administrative feasibility. The number of toxic substances subject to regulation seems very large. Regulation of so many substances could well be extremely difficult if EPA were precluded from drawing inferences from available data on well-known, related substances. Moreover, requiring proof of causation for each chemical would force EPA to expend resources in areas that are well-enough known so that inference is acceptable, when those resources could be otherwise employed in areas where knowledge is inadequate. In ruling on the type of proof and procedure required for making individual determinations, the Supreme Court has construed statutes protecting the environment and public health in light of considerations of administrative feasibility. See *E. I. du Pont de Nemours & Co.* v. *Train*, 430 U.S. at 132 (type of proof);[82] *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 62–22 (1973) (procedure).[83] See also *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192, 202–05 (1956).

[82] The Supreme Court stated in E. I. du Pont de Nemours & Co. v. Train, 430 U.S. 112, 132 (1977) (quoting Permian Basin Area Rate Cases, 390 U.S. 747, 777 (1968)): * * * (C)onsiderations of feasibility and practicality are certainly germane" to the issues before us. Bowles v. Willingham, (321 U.S. 503,) 517. We cannot, in these circumstances, conclude that Congress has given authority inadequate to achieve with reasonable effectiveness the purposes for which it has acted.'

[83] The Supreme Court stated in Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 621 (1973), holding that individual proceedings were not required for each of the thousands of drugs subject to regulation:

"The NAS–NRC panels evaluated approximately 16,500 claims made on behalf of the 4,000 drugs marketed pursuant to effective NDA's in 1962. Seventy percent of these claims were found not to be supported by substantial evidence of effectiveness, and only 434 drugs were found effective for all their claimed uses. If FDA were required automatically to hold a hearing for each product whose efficacy was questioned by the NAS–NRC study, even though many hearings would be an exercise in futility, we have no doubt that it could not fulfill its statutory mandate to remove from the market all those drugs which do not meet the effectiveness requirements of the Act."

OSHA believes that the combination of the broadly based rulemaking hearing and proceeding concerning this proposal and the subsequent section 6(b) proceedings on individual substances will provide all parties with ample opportunity to present their views and comments at the most relevant procedural stages. Certain policy determinations will be limited but not foreclosed from rehearing at the subsequent section 6(b) hearings. Other decisions based more on factual considerations, such as the applicability of the content of the specific protective provisions such as monitoring, respirator use and protective clothing, are open in the section 6(b) proceedings

depending on the unique properties of the substance being regulated, as is pointed out below.

The Supreme Court has indicated, that when applying the Storer Doctrine, it is appropriate to permit participants in individual proceedings to be able to petition for a modification of the general policies. However, the participant would have to meet a heavy burden of proof to show justification for the modification. Some participants have argued that the proposed cancer policy did not have adequate provisions to permit persons to petition to modify the general policies (AIHC Ex. 251A, pp. 46–47). Other participants argued there were adequate provisions in the proposal or that such provisions were not necessary when the policies were to be applied in a subsequent rulemaking and not an adjudication. (C. 270, pp. 13–14). The final cancer policy has been changed to permit more extensive provisions to petition for modifications of the general policies. Sections 1990.106 and .145 provide for procedures for petitioning to modify the general policies included in the cancer policy. Section 1990.145 permits such petitions in the course of a rulemaking on an individual substance if strong new evidence become available. Section 1990.144 permits consideration of certain issues if meeting certain criteria evidence is presented.

Therefore, OSHA believes the flexibility and fairness of the individual substance-by-substance approach will be preserved by the procedures and policies incorporated in this part since the feasibility and appropriateness of the protective provisions as applied to a given substance will be fully discussed at the rulemaking concerning the specific substance, held pursuant to this Part. Yet OSHA's general policy and factual judgments, based mainly "on the frontiers of scientific knowledge" with a "command to act", have been established after opportunity for full public participation in this rulemaking, and any future amendments thereto, and will not be allowed to be relitigated in "the standard-by-standard", "substance-by-substance" or "case-by-case" process.

The Cancer Policy is an occupational safety and health standard within the meaning of the Act. It contains scientific policy determinations, regulatory procedures, and specific provisions which will be included in the regulation of potential carcinogenic substances. These provisions include, for example, the requirement that exposures be set at the lowest feasible level and that there be primary reliance on engineering and work practice controls. Some provisions of the model standard are also presumptively required. Thus, some issues normally raised and considered in section 6(b) standards setting proceedings have been limited or resolved in this rulemaking. Therefore OSHA has followed the additional procedural requirements specified by section 6(b) of the Act and the OSHA procedural regulations in 29 CFR Part 1911 for issuing occupational safety and health standards.

On September 11, 1978, the Secretary of the United States Department of Health, Education and Welfare publicly introduced a draft scientific study prepared by the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS) and the National Institute for Occupational Safety and Health (NIOSH) entitled: "Estimates of the Fraction of Cancer in the United States Related To Occupational Factors" (NCI, NIEHS and NIOSH Institutes' Report). The final report was introduced into the Record of this rulemaking on September 15, 1978 and is discussed below. OSHA believes that in presenting the NCI, NIEHS and NIOSH Institutes' Report, the Secretary of HEW's remarks are particularly relevant in setting this rulemaking in its proper context. The Secretary of HEW stated:

". . . most of the arguments against occupational health and safety measures, as you know, focus on costs. And these arguments seldom focus on the tremendous gain that these programs can provide.

"It is, in my judgment, myopic to argue that programs to protect workers are inflationary—if we do not count in our calculations what those programs buy: safety, health and often greater productivity.

"It is time to take the blinders off: To count what these programs promise in ultimate savings. Which, after all, creates the greater burden: the cost of a program to protect workers from occupational hazards? Or the staggering costs of treating workers for the consequences of these hazards? Our economists must join with our scientists and find a new way to calculate inflation related to occupational health and safety.

"Finally, there is the matter of simple justice. We do not want an economy that buys goods at the expense of workers' health; an economy that asks workers to earn their livelihoods by endangering their lives. The workers of America are willing and able and eager to sweat on the job; we should not ask them to bleed.

"So you and I have a job to do; a job of convincing the American public that programs of prevention and health promotion are not just an expense, but an investment; that they are worthwhile, desirable, economically feasible, and urgently needed—especially in the workplace. For it is in the workplace where many of the dangers are greatest.

"And vigilance in the workplace is one way of detecting hazards that may otherwise spread from factory or laboratory to the world outside. We have learned, often by tragic experience, that kepone, undetected in the workplace today, flows insidiously into our rivers and streams tomorrow. The occupational exposure to asbestos today is tomorrow's exposure to our families at home and our children in school. Today's chemical dumping ground may be tomorrow's subdivison or school playground. By protecting workers today, we are likely to make the greatest gains in our efforts to protect the rest of society.

"So I would argue first that we should take a broad view of occupational health and safety programs. These are not programs which benefit workers alone—they are for all of us. So they belong at the center of a broad new national preventive-health strategy."

III. CANCER AS A PUBLIC HEALTH PROBLEM AND A PUBLIC POLICY DILEMMA

Cancer is a particularly dreaded and costly disease. It is believed that almost 400,000 Americans died of cancer in 1977—more than 1,000 persons per day. Over one million Americans are under treatment for some form of the disease, and each year over 900,000 new cases are diagnosed in this country. Of these cases, about one-third are skin cancers: troublesome, sometimes painful, usually treatable, causing the death of about 2,000 persons per year; the other two-thirds or 600,000, however, are more serious and more of them are potentially fatal. About 25 percent of the United States' population—one person in four—will ultimately develop some form of cancer, other than skin cancer. Despite enormous expenditures on research into methods of treatment, the survival rates of patients afflicted with most of the major types of cancer have improved only a little during the past 20 years. Thus, most persons contracting cancer die within 2 or 3 years—often after expensive, painful, and distressing illnesses (USDHEW 1973, 1975, 1977; American Cancer Society 1978).

As other causes of death have declined in frequency, cancer has increased in importance and is now the second most frequent cause of death in the United States. Although cancer accounted for less than 4% of deaths in the United States in 1900 (64 deaths per 100,000) it accounted for more than 18% in 1975 (170 deaths per 100,000) (crude rates) (National Center for Health Statistics, 1970; American Cancer Society 1978; Epstein, Univ. of Illinois, S. 4). The increase in the mortality rate from cancer is due in part to aging of the population and in part to increases in age-specific mortality rates (Epstein, Univ. of Illinois, S. 5; Jones, Univ. of San Francisco, S. 22–50). After adjusting for

changes in age distribution of the population, cancer incidence rates in the United States have been increasing during this decade at about 2% per annum (Schneiderman, (NCI), Post-Hearing Comment, pp. 2–3). However, the trends in cancer incidence and mortality are complex: when analyzed in detail, they show a complicated pattern of increases and decreases, depending on many factors such as anatomical site, age, sex, socio-economic status and geographic location. (Berg, Colo. Regional Cancer Center, S. 6–8; Schneiderman, NCI, S. 3–7; Jones, Univ. of San Francisco, S. 22–50; Epstein, Univ. of Illinois, S. 6–8). In recent years, there have been increases in the incidences of cancer of the breast, colon, prostate, bladder, lung, pancreas, esophagus, skin (melanoma), and lymphatic system. As shown in detail in subsequent sections, some of the increases are attributable in part to cigarette smoking and to occupational factors, sometimes acting together (see Sections G-H below).

The economic and social impacts of cancer in the United States are massive and yet hard to estimate. Certainly the human anguish is. Those impacts, however, are very real. The National Center for Health Statistics estimates that by 1977, the Nation was spending $5.5 billion each year on hospital care and physicians' services for cancer patients and that the expected earnings of people who died that year had a value of $14.6 to $18.5 billion. Additional costs such as outpatient therapy and other treatment-related fees may raise the direct annual expenditures for cancer well into the tens of billions of dollars. To these direct expenditures must be added indirect costs, such as the estimated 1.8 million work-years lost annually to the national economy and to family income by unemployed or underemployed cancer victims (Levin, D. L., *et al.*, 1974). Another estimate cited by the General Accounting Office of the United States Congress is that the annual cost of cancer is at least $15 billion, of which $3–5 billion is attributable to direct care and treatment and the remainder to the loss of earning power and productivity (GAO 1976). This estimate is supported by a study prepared with information on the economic costs of cancer to the United States, and to individual patients' families in particular. See "The National Cancer Program, the Strategic Plan", January 1973.

Cancer is a disease exceptionally feared by the American people, apparently because of its unique manifestations: the progressive and irreversible destruction of the body by autonomous growth of abnormal cells from within the body itself. Moreover, it is sometimes stated that cancer is a disease which affects the survivors as much as the victims (Wilson, Harvard Univ., S. 37.). Thus, although it is sometimes claimed that cancer is primarily a disease of old age and that its elimination would not increase life expectancy by more than a few years, the Nation has expressed a special determination to control cancer, by expending large sums on research, treatment, and rehabilitation. More recently, with the recognition that measures to reduce exposures to substances that cause cancer may be more effective in eliminating this disease than attempts to cure it, the Congress and the research and regulatory agencies have begun to devote more of the Nation's resources to prevention of cancer by the reduction of human exposures to such substances. Some parties to this proceeding recognized such efforts, such as API which stated: ". . . because our massive research efforts have produced few clear solutions, the progress of a cancer is frequently irreversible. Under the circumstances it is both appropriate and necessary that we place substantial emphasis on cancer prevention. This should include efforts to control and reduce possible exposure to carcinogens in the environment, including the working environment." (API Post-Hearing Brief, Appendix C, p. 1).

A. THE NATURE OF THE DISEASE

Cancer is a disease generally characterized by the progressive growth of abnormal populations of cells. The early cellular and molecular events of the disease and the mechanisms leading to its initiation are not fully understood, although progress has been made as a result of research in recent decades. Some of the results of this research were presented in testimony or exhibits at the hearing; e.g., in the statements of Dr. Emmanuel Farber (Univ. of Toronto), Dr. Curtis Harris (NCI), Dr. Benjamin Trump (Univ. of Maryland), Dr. Ronald Hart (Ohio State Univ.); Dr. Francis Roe (AIHC), and in such exhibits as the symposium volumes *Origins of Human Cancer* (Hiatt *et al.*, 1977). Much of this evidence supports the theory that cancer originates from cells which have been transformed, frequently by changes in or damage to the DNA or other genetic material. Although such damage to DNA may frequently be repaired, permanent cell transformation may result if the repair mechanisms are ineffective, or if the damage is repaired incorrectly. There is increasing evidence that at least some cancers may originate from a single transformed cell. Once the initial transformation has taken place, the resulting aberrant cells are capable of self-replication and may progress to stages in which they are capable of invading normal tissue, and spreading throughout the body, even though the agent or agents responsible for inducing the disease may be no longer present.

In most cases of cancer, unrestrained cell growth leads to the development of *tumors* which compress, invade, and/or destroy normal tissues. These tumors usually lead eventually to death. Just as there are many different types of cells in the body, there are different types of tumors, each of which may be distinctive in its behavior. However, induced malignant tumors generally share some common characteristics, such as a long latent period between initial exposure and manifestation of the disease, as pointed out below. Some other characteristics may also include a higher rate of cell growth than in the normal, surrounding tissues, failure to maintain the boundaries of normal tissue and organs, a microscopic appearance which suggests immature rather than mature tissues, and a tendency in humans to spread to parts of the body distant from the original site of the cancer. Not all of these features, however, accompany every malignant tumor.

Most body structures are composed of many different kinds of tissues made up of many different types of cells, any of which may give rise to cancer. A specific type of cancer draws its name generally from the type of cell affected. For example:

- Cancers of connective tissue, including bones, are generally called sarcomas.
- Cancers of epithelial cells that line the body's internal surfaces and cover the external surfaces (lung, breast, skin, etc.) are generally called carcinomas.
- Cancers of cells that compose the blood-forming system are generally called leukemias or lymphomas.

Although sarcomas, carcinomas, and lymphomas share many common characteristics, epidemiological studies have revealed differences in their behavior which suggest that at least some of the factors controlling their development may differ (Peto 1977, pp. 1410–1411). The vast majority (over 90%) of fatal human cancers are carcinomas, so that most generalizations about "cancer" and its mechanisms are actually generalizations about carcinomas (*id.*). Indeed, the word "cancer", although now used generally for all types of malignant neoplasms

originally applied specifically to carcinomas.

Cancer is a collective term for large number of different types of disease. Therefore it is difficult to specify features that uniquely characterize cancer or even to give the term a rigorous scientific definition. Dr. Harold Stewart (NIH) discussed the problem involved in defining cancer:

"More than 100 years ago, Professor Virchow opined: "I do not think that a living human being can be found who even under torture could actually say what tumors really are." But even today, in the face of Virchow's warning, imposter savants continue the production of inaccurate and inapplicable definitions of cancer. Some feel that such definitions are too pragmatic and do damage by discouraging new concepts and are thus a real impediment to cancer research. From a practical point of view, they inhibit the recognition of early or so-called borderline cancers in laboratory animals. According to Nemerov: "People's reason for wanting a definition is to take care of the borderline case, and this is what a definition, as if by definition, will not do." (Stewart, 1977, pp. 306–307; Exhibit C to Stewart Statement, references omitted.)

Definitions of terms such as "neoplasm" were also discussed by Dr. I. Nathan Dubin (Medical College of Penn., S. 4–5):

"*Neoplasm.* One of the shortest definitions of '*neoplasms*', and still accurate, was given by the American pioneer in cancer, James Ewing (1928, p. 5); he defined it as follows: 'A tumor [1] is an autonomous new growth of tissues.' Willis (1948, p. 1) stated that a neoplasm was 'an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change.' In other words, a neoplasm is a new mass of multiplying cells which have escaped from the normal controls of the host and which are independent of those mechanisms that normally control the number, multiplication, histological structure, and metabolism of normal cells."

[1] For "tumor" substitute the word "neoplasm", currently preferred.

Dr. Emmanuel Farber (University of Toronto) offered a generalized definition of cancer:

". . . I do not belong to that group who advocate we abandon the word 'cancer' for something more precise. Precision is essential for scientific analysis. Yet, the essence of the cancer problem is just that—we do not know what the components are that allow the cellular behavior we see. Until we know that, we had best use an imprecise term, otherwise, we are just as likely to pick a wrong precise one. In the context of this presentation, 'cancer' is an imprecise descriptive term to encompass all the many conditions in which cells proliferate for whatever reason in a more or less uncontrolled manner, invade tissues and set up satellite growths in other organs. The overall result of such a process, if left undisturbed, is almost always the death of the host." (Farber, 1973, pp. 4–5; Appendix B to Farber Statement.)

However, despite the difficulties of definition, both Dr. Stewart (NIH) and Dr. Farber (Univ. of Toronto) emphasized that cancer can almost always be readily identified and diagnosed as such. Dr. Farber stated:

"What do we know about the essence of how a malignant neoplastic cell differs from its normal homologue? I must stress at this point that cancer is not a unity but rather a whole biological spectrum which varies quite widely with the nature of the tissue and cell involved as well as with the physiologic state of the host. Yet, despite this spread, most examples of malignant neoplasia do fall fairly easily into a category that allows one to classify them as cancer.

"As stated clearly by Prehn (87), neoplasia comprises two separate alterations in cell physiology: (1) a form of abnormal somatic cell variation that represents somatic mutation and/or aberrant and defective differentiation, and (2) a pathologic form of hyperplasia. . ." (Farber, 1973, p. 5; Appendix B to Farber Statement.)

And Dr. Stewart stated:

"From years of experience, the clinical pathologist has learned to distinguish early neoplastic lesions from simple hyperplastic changes, and vice versa. Thus, although they look much alike through the microscope, the papillary lesion in the larynx of juveniles will, he knows, regress spontaneously, whereas that in the urinary bladder will, if untreated, progress to widespread cancer. Many comparative pathologists lack this degree of sophistication. Either they ignore or they fail to recognize the potentialities of the innocent-looking cellular proliferations that often herald the development of neoplasms in laboratory rodents. One example is the common pulmonary neoplasm of the mouse that arises from the alveolar type-II cell. Some misapply the terms "alveolar cell hyperplasia" or "adenoma" to its early developing stages. Later, however, after the growth has reached large proportions, or spread to the pleura and mediastinum or metastasized, they then apply the term "cancer." The neoplasm, excised at different stages in its development, grows readily when transplanted to syngeneic mice, in which it exhibits autonomy, invasion, and metastases. Application of the term "hyperplasia," which implies a nonneoplastic process or "adenoma," which implies a benign tumor, to any stage in its biologic development and progression represents misuse of these terms." (Stewart, 1977, pp. 305–306; Exhibit C to Stewart Statement.)

Dr. Francis J. C. Roe (AIHC) defined cancer as follows:

"Cancer is a disease of multicellular organisms which is characterised by the seemingly uncontrolled multiplication and spread within the organism of apparently abnormal forms of the organism's own cells."

* * * * *

"Within this definition are mentioned the three key characteristics of cancer—cellular multiplication, invasiveness and autonomy.

"It would not be possible to define cancer in terms of cell multiplication only, firstly because the cell generation-time in some cancers is long compared with that in normal tissues such as the gut mucosa and bone marrow. Secondly, the rapid multiplication of cells which had not acquired the ability to invade surrounding tissues would lead to an easily-treated, benign tumour rather than to a malignant one.

"Invasiveness is the characteristic of cancer which makes it a lethal disease. It is interesting, in this connection, to make a distinction between cancers of solid tissues and cancer of the blood or lymphatic systems. In the latter case, the normal cells already have the ability to invade other tissues, and the cancerous state arises when the rate of production of new cells continually exceeds the rate of destruction of old ones.

"Autonomy refers to the apparently uncontrolled nature of cell multiplication. It is supposed that, in the normal way, during development and repair, the overgrowth of tissues or cells is resisted by the organism as a whole or by the affected tissues or organs. Cancer represents an escape from such control. Our knowledge of controlling mechanisms is far from complete . . ." (Roe, S. 15, quoting Roe, 1966a)

Dr. Roe testified further:

"Although cellular abnormality is usually an integral aspect of the cancerous process, it is important to stress that *cancer is a disease of the whole of multicellular organisms and not a disease or disorder or cells . . .*". (Roe, S. 16, emphasis in original)

Other witnesses such as Nobel Prize winner Dr. David Baltimore (Massachusetts Institute of Technology), emphasized that cancer is a disease of cells (Baltimore, S. 1). In fact, as made clear by Dr. Roe, it is both: cancer is a disease affecting organisms which is characterized by and caused by abnormal behavior of their cells.

B. THE MULTI-STAGE, MULTI-CAUSAL NATURE OF CANCER

Many witnesses emphasized that cancer is a complex disease which characteristically progresses through a number of stages of development, and that a variety of different factors can act to initiate or accelerate its development at each stage. It follows from this proposition that most cancers would have multiple "causes" and that it therefore would be simplistic to assign to each a single causative agent. In the regulatory context, this does not mean however that the task of prevention is irrelevant or hopeless. Indeed, it makes it even more imperative to prevent or reduce exposures to known carcinogens for we do not know the interactions of other and unknown variables, such as

genetic, hormonal or synergistic factors in any given individual or population.

In recognition that cancer may evolve from multiple causes, Dr. Arthur Upton (Director, NCI) made the following summary characterization:

"It is no longer held likely that cancer results from a single factor; rather it appears that carcinogenesis is a multi-causal, multi-stage process, in which several environmental factors as well as other influences, such as genetic and hormonal factors, play varying roles in a particular carcinogenic response. Even within the group of factors commonly labelled "environmental," it seems that in many cases several different factors interact to induce cancer. Certain agents initiate neoplastic cell transformation; others act as "promoters" or "co-carcinogens"; others may enhance the metabolic activation of procarcinogens. Some agents act on DNA; some activate latent viruses; others may accelerate the development of cancer cell lines by modifying hormone levels, or by suppressing immune mechanisms. These various environmental factors may interact not only with each other, but with genetic, nutritional, and hormonal factors in the host, to influence the probability of developing cancer. It is, therefore, impossible to identify a single "cause" for each case or type of cancer." (Upton, S. 3–4)

Dr. David Rall (Director, NIEHS) made the following statement:

". . . recent research on the mechanisms of carcinogenesis has shown that it is a complex process which progresses through a number of stages. First, the precarcinogen (which is usually chemically unreactive) is converted to a reactive electrophilic intermediate: This conversion requires one or more metabolic reactions whose rates depend on the activity of enzymes and other factors in the cell. Second, this reactive intermediate interacts with electron-rich centers in the target cell (usually in the DNA) to cause cell transformation. This change in DNA may be reversed by the process of DNA repair, or may lead to the successful initiation of a transformed cell line. The new cell line may or may not develop autonomously to form a tumor, depending on enzyme activities, hormone levels, the effectiveness of immune mechanisms, etc. Each of these stages in carcinogenesis may be initiated, promoted, or modified by a variety of host and environmental factors, including chemicals as well as diet, hormones, etc. It thus appears that the initiation and development of a tumor are affected by a number of factors, acting simultaneously or sequentially, and it is erroneous and meaningless to assert that they are "caused" by only one . . .". (Rall, S. 4–5).

Dr. I. Bernard Weinstein (Columbia University) expressed the concept as follows:

"We know that in both experimental animals, and in humans, carcinogenesis frequently results from the exposure not to a single substance but to several substances and that the evolution from a normal cell to a tumor cell is a multi-step process with different agents acting at different stages. It is possible to define at least two different types of agents as well as two distinct steps. The first types of agents are called initiating agent carcinogens, and are sometimes referred to as "solitary carcinogens." These compounds, when given at sufficient doses, produce tumors on their own. They also are frequently mutagenic when tested in mutagenesis assays." (Weinstein, S. 6)

Dr. Robert Squire (Johns Hopkins University) made a similar statement and showed how the multi-stage, multi-causal nature of cancer frequently results in synergistic action between causative agents:

"Epithelial cancer, for example, as is now recognized, involves a multistage process in which sequential cellular and subcellular events precede the appearance of clinical cancer. To describe this process, the concepts of "initiation" and "promotion" have been introduced in studies of carcinogenesis in skin (Berenblum 1941). These prevail today and are considered relevant to many other epithelial systems (Farber 1976; see also Appendix B). "Initiation" describes a specific, irreversible cellular alteration induced by carcinogenic substances and resulting in a population of latent or dormant tumor cells. "Promotion" describes the proliferation of those cells, which is induced by subsequent exposure to the same or a different substance and which results in a progression to clinical cancer. Classical initiation-promotion studies illustrate well the synergistic effects of separate exposures neither of which alone would have produced cancer at the doses involved. Significantly, the conditions induced by initiator substances persist, and therefore exposure to a promoting substance even after a considerable delay can result in cancer (Berenblum 1974; Boutwell 1974, 1976, 1977).

"Studies involving liver carcinogenesis have also shown persistent and additive effects of subcarcinogenic exposure to certain substances. Becker (1975) demonstrated that cellular alterations induced by subcarcinogenic doses of N-2-fluorenylacetamide may later be augmented by subcarcinogenic doses of dimethylnitrosamine or N-hydroxyfluorenylacetamide to yield hepatocellular carcinoma. Weisburger et al. (1965) showed an increase in liver cancer induction after combined exposure to 2-acetylaminofluorene and carbon tetrachloride.

"In other systems, the studies of nitrosomethylurea and cyclamate by Hicks et al. (1975) and the Oser study (Oser et al. 1975) of cyclamate and saccharin demonstrated at least additive if not synergistic effects of two substances in the induction of bladder cancer in rats. Laskin et al. (1970) demonstrated that benzo(a)pyrene combined with sulfur dioxide, when inhaled, induced lung cancer in rats. In the doses administered, neither substance alone was carcinogenic.

"Other examples of cocarcinogenesis in animals exist in the literature; there is also evidence that cigarette smoking and occupational exposure to asbestos have synergistic or additive effects in humans (Selikoff et al. 1968). It must therefore be assumed that cocarcinogenesis is not rare in humans or animals. (Squire, S. 5–7)

Dr. Emmanuel Farber (Univ. of Toronto) presented testimony and exhibits which described in detail the progression of cancer through a series of stages, using his own research on liver carcinogenesis as examples:

"Figure 1 of Appendix D illustrates our current views of the major steps in liver carcinogenesis initiated by chemicals, including an approximate estimate of the relative time scale of these steps in the process. We think that the preneoplastic phase, including initiation, takes up well over 50 percent of the whole in the liver and this fits well with what we know in many other organs and tissues, including some in humans (lung, skin, liver, urinary bladder, etc.). Initiation is quite rapid and consists of at least two steps—the induction of some one or more molecular alterations as the first step, and a round of cell replication for "fixation" as the second step. A delay in the time of occurrence of the second step may favor the reversibility of the first step by repair processes. This is followed by a long period dominated by selection and growth of the putative initiated cells and the progressive differentiation of these cells (see pp. 4–6 in Appendix C, and pp. 11–12 and Charts 1–7 in Appendix B.). Neoplastic development resembles a chain reaction, triggered by exposure to a carcinogen, in which the links are new cell populations with altered organisational, structural, and biochemical properties. The probability that the new cell populations will be transformed to a malignant state increases progressively through a number of stages (Charts 6 and 7 in Appendix B).

"Most chemical carcinogens appear to inhibit cell proliferation, as reflected in the fact that they inhibit regeneration of liver cells following partial hepatectomy. This creates an environment in which there is selection for cells with resistance to the cytotoxic action of the carcinogen. (Chart 4 of Appendix B). In one of our experiments, we have shown that administration of such a cytotoxic agent (2-acetylaminofluorene) permitted the selective growth of foci of resistant cells previously transformed by a single exposure to another carcinogen (diethylnitrosamine) (Appendix E). In subsequent steps of development, exposure to one or more carcinogens may lead to selection for resistance, growth, and increasing malignancy of the transformed cell population (Chart 4 of Appendix B).

"There are thus at least two ways in which chemicals can lead to the development of cancer: by initiating changes in cells and by permitting selective growth of populations of changed cells. Some chemicals, of course, may act in both ways. The experimental technique described in Appendix E shows how the two types of actions may be detected and studied independently. It appears very promising as a short term test for carcinogenicity, at least in the liver.

"The fate of cells altered by exposure to an initiating dose of a carcinogen is largely

environment dependent. If this is appropriate for selective growth, cancer develops. If this is not, no cancer may develop in the lifetime of that organism even though the initiated cells may persist for a major portion of its life span. Carcinogens or probably noncarcinogenic promoting agents play a major role in creating this selection of environment (Appendix D, pp. 19–21).

"As our knowledge of the sequences of events involved in carcinogenesis increases, we can no longer regard chemical carcinogenesis as a simple one-stage or two-stage process. Rather, cancer seems to develop progressively through a number of stages, each of which can be influenced by chemicals or other environmental factors, interacting with host factors such as nutrition, hormone levels, etc. Any proposal for identification and classification of carcinogens should recognize this complexity. (Farber, S. 2–4, citing Farber 1973, Farber, *et al.* 1978, Farber, 1978, Solt and Farber, 1976; Appendices B, C, D, E to Farber Statement)

"Another facet that I think is important to emphasize in this context is that the biological properties that seem to be characteristic of cancer are not necessarily a single unitary package of biological aberration but rather seem to be a number of discrete units that can be acquired separately during its life history. This concept of progressive acquisition of the alterations that go to make up a neoplasm at any stage in its evolution is, in my view, a fundamental one that I shall return to later in greater detail."

* * * * *

"Given a plethora of potential carcinogenic stimuli and a susceptible host, how does cancer develop? There is almost universal agreement that more than one step is essential before we can observe with any method now available an identifiable cancer. This step-wise process is best observed in the skin with chemical carcinogens (6–8, 104) but is now amply documented in many different systems in man and in animals. Although instances of a direct conversion of a normal target cell to [a] growing cancer may be found, the majority of examples so far studied indicate a more complex process.

"The initial interaction between a chemical carcinogen or one of several forms of irradiation and the target tissue may be of very short duration and irreversible. We are now beginning to obtain some insight into this phase, *initiation* and I shall return to this shortly. The subsequent steps are still very much unclear. There are at least two major possibilities: (1) the first states that the process of initiation induces a cancer cell and that all the subsequent steps, however many they may be, are concerned with encouraging the growth of this cellular species. In other words, according to this hypothesis, the problem is essentially the development or evolution *of* a cancer cell (Chart 1). (2) The alternative hypothesis states that the process of initiation induces an altered but non-neoplastic cell that now can evolve into cancer, acquiring seriatim as it does the properties that endow the cancer with its characteristic behavior pattern. In other words, according to this second hypothesis, the problem is the development or evolution *to* a cancer cell (Chart 2). This whole process leading to the first appearance of a malignant neoplastic cell population, together with the subsequent evolution of an already formed cancer, would all be included in what Foulds calls *progression* (31). Although these distinctions between (1) and (2) may seem trivial, they are far from it, both theoretically and especially practically. How one would attempt to analyze the process in order to prevent the appearance of a cancer could differ greatly depending upon which hypothesis one subscribes to.

"If a multistep process is the usual, what is its meaning in relation to cancer? What is the essential need for a series of steps, each probably occurring in a new cell population, in the development of a malignant neoplastic process? The simplest hypothesis states that a cell or group of cells that display all the major properties we associate with cancer have several "biological units" of aberration or deviation from the original target cell population and that each of these units is usually acquired separately in a new cell population in a stepwise fashion (Chart 3). Although, conceivably, some circumstances may exist whereby all the units can be induced simultaneously, this appears to be the exception rather than the rule, at least with chemical carcinogens, irradiation and the inert plastic sheets. If this concept has any validity, we would anticipate as a minimum 3 or 4 major steps, since growth, invasion, metastasis and cytologic alteration appear to be easily recognizable characteristics of many forms of cancer (see 57).

"Obviously, these are only gross behavioral properties of a malignant cell population. There must be many more alterations when one views the population at metabolic and molecular levels. In addition, each property has a quantitative range, often very wide, so that growth may be slow or fast, invasion may be minimal or extensive, etc. This is seen clearly not only in cancer of different tissues but also in cancer of the same type at different phases of its development.

"This view of carcinogenesis implies that the transformation of an original target cell population to an overt cancer consists of a number of discrete cell populations, each of which in their makeup and properties is one step closer to the final goal. In other words, carcinogenesis may be nothing more or less than equivalent to a process of progressive cellular evolution which stops only with the demise of the host. (Farber, 1973, pp. 10–14; Appendix B to Farber Statement.)

"It is now clearly evident that the development of cancer in many, if not all epithelial tissues as well as in some connective tissue and other mesodermal and non-epithelial ectodermal cells and tissues, is a multistep process. In this process, new cell populations appear with altered phenotypic properties and at least some of these new cell types appear to participate as steps in a sequence of events leading to cancer (malignant neoplasia). These collections of new cells are often highlights in the process. The identification and characterization of these various cells and the delineation of their role in the development of cancer remains as a major challenge, not only as essential components in evolving an understanding of the nature of a malignant neoplasm, but also as a basis for new approaches to the early diagnosis of preneoplasia and neoplasia and to the interruption of the carcinogenic process." (Farber, 1978, p. 2; Appendix D to Farber Statement.)

Dr. Farber's work is described more fully in his exhibits and was referred to by a number of other witnesses. (See, for example, Dr. Kotin, Johns-Manville, S. 12). Two distinctive features of Dr. Farber's conclusions are: (a) that the probability that a transformed cell will eventually progress into a tumor is initially low but increases at each step in the process of development; (b) that some agents increase this probability by exerting selection in favor of the transformed cells relative to normal cells.

Mr. Richard Peto (Oxford University) discussed multistage models for carcinogenic development and showed that they are consistent with and derive considerable support from the results of epidemiological studies:

". . . it seems likely that multistage processes underlie the generation of a large majority of human cancers (the carcinomas). . . . Although the eventual synthesis is not yet in sight, multistage models should at present be thought about to some extent, and their general features should be common knowledge, as the general framework of this eventual synthesis will (at least for that 90% of fatal human cancers which are carcinomas) almost certainly be some kind of multistage model.

* * * * *

"The essential multistage hypothesis is that a few distinct changes (each heritable when cells carrying them divide) are necessary to alter a normal cell into a malignant cell, and that human cancer usually arises from the proliferation of a clone derived from a single cell that suffered all the necessary changes and then started to proliferate malignantly." (Peto, 1977, pp. 1403–1404; Annex D to Peto Statement.)

As pointed out by most of the above witnesses, the fact that cancer can be a multistage process in which each stage can be influenced by internal and external factors means that most cancers are likely to have multiple causes. Mr. Peto discussed this relationship between multiple stages and multiple causes, using data on human lung cancer to support his conclusions:

"If multistage models are even approximately true, then the incidence rate for each cancer is proportional to a product of more than one event rate, each with different determinants, and it makes little sense to ask for the cause of a particular cancer; each has more than one distinct cause."

* * * * *

"In general, it seems that different stages in carcinoma induction have qualitatively different causes and are therefore themselves qualitatively different from each other". (Peto 1977, pp. 1420, 1422; Annex D to Peto Statement.)

Dr. Francis Roe (AIHC) presented a summary of the various factors known to influence cancer incidence in experimental animals. These factors include genetic factors, viruses, hormones, microbiological status, immunological status, parasitic infections, trauma, burns, actinic radiation, ionizing radiation, caloric intake, and diet, in addition to chemical carcinogens (Roe, S. 20–41). It is important to note that almost all of these factors are known to affect cancer incidence in humans as well as in experimental animals (for examples, see reviews in Fraumeni, 1975).

Many other witnesses added specific or general comments emphasizing the multi-causal aspects of cancer. For example, Dr. Marvin Schneiderman (NCI) quoted from the Report of the Safe Drinking Water Committee:

"A possibly unifying concept concerning interactions is the "*fertile ground*" idea. If the carcinogen falls on fertile ground, it will lead to cancer growth. If not, no cancer. This implies a whole set of questions about the nature of the "fertile ground." Some animal experimentation seems to imply that, with the induction of mammary tumors in the rat by hormonal stimulation, the ground is made fertile by earlier viral infection (Shellabarger, 1976). Similar results seem to be shown in the induction of (mouse) cancers through the combination of malaria infection and exposure to the Moloney mouse-tumor virus (Wedderburn, 1970). A similar mechanism has been suggested for the development of Burkitt's lymphoma in children in East Africa, in malaria infection associated with appropriate viral infection (Morrow, 1976).

"Another way that fertile ground can arise is through a deficiency interaction. Here, the absence of some element, material, or vitamin may reduce the ability of repair mechanisms, so that a level of a carcinogen that produces little or no cancer in a population capable of repair produces much cancer in a population of repair-deficient individuals. An example is the high cancer rate in Xeroderma pigmentosum patients—people with a low ability for DNA repair (Robbins, 1974; Cleaver, 1968). A similar mechanism (on a grosser level) may be involved in the high incidence of cancer of the esophagus in central Asians, whose bread and tea diet may not contain the elements necessary to permit repair of tissue affected by low levels of a nonidentified carcinogen (Mahboubi, 1973)." (NAS, 1977a, p. 51).

Dr. Arthur Upton (Director, NCI) cited lung cancer as an example of a multi-causal phenomenon:

"Cigarette smoking provides an example of the difficulty of quantifying the contribution of a single factor, even in an apparently clear-cut case. The incidence of cancer in smokers and non-smokers has been studied extensively; the excess rates of cancer in smokers are well established; and from knowledge of the number of smokers the total number of excess cancers causally *related* with smoking can be calculated. For example, it has been estimated that up to 40 percent of all male cancer deaths in the U.S. (i.e., about 85,000 deaths annually) may be associated with cigarette smoking. It would be reasonable to conclude that smoking is *one* major cause of these cancers, in the sense that they would not have occurred in the absence of smoking. However, it would not be reasonable to conclude that smoking is the *only* cause. It is known, for example, that at least two agents—alpha-radiation and asbestos—act synergistically with cigarette smoking in causing lung cancer in exposed workers. In addition, work to be summarized in the testimony of Dr. Curtis C. Harris of NCI has shown that there is much inter-individual variability in the susceptibility of human cells to carcinogenic agents found in tobacco smoke. Thus, the effect of cigarette smoking in inducing cancer is known to be dependent on physical, chemical, and host factors; however, we do not know the degree to which it is dependent on these factors (or on other factors which may be uncovered in the future). Hence, we cannot assert that the 40% of male cancer deaths in the general population associated with smoking are not simultaneously associated with one or more other factors." (Upton, S. 4–5)

Dr. Robert Squire (Johns Hopkins University) gave a similar example:

"However, there is also reason to be concerned about interaction between environmental factors and genetic predisposition in segments of the population. An example is the association between genetically determined aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma (Kellerman 1977)." (Squire, S. 4)

Dr. David Rall (Director, NIEHS) also referred to the same example:

"For example, there is increasing evidence that the carcinogenicity of benzo(a)pyrene is strongly affected by characteristics of the host animal, including the activity of enzymes which convert the chemical to active metabolites, and perhaps by conditions in the gut which lead to reactivation of the ultimate carcinogen. These characteristics are believed to be influenced by genetic and dietary factors respectively. It would be wrong to assert that a particular cancer (or class of cancers) is "caused" by genetic factors, or "caused" by dietary factors, or "caused" by benzo(a)pyrene. The occurrence of the cancer is attributable to all three factors (and probably others) acting in combination." (Rall, S. 5)

Dr. Rall continued:

"Recognizing that carcinogenesis is a multi-phased process whose progression is influenced by a number of different factors, it makes little sense to assert that "only" 1–5% of cancers are attributable to a single factor. It would be consistent with our present knowledge to assert that *all* cancers are associated in one way or another with occupational factors, just as they are probably *all* associated with dietary factors, with genetic factors, and with hormonal factors." (Rall, S. 5)

C. INTERACTIONS AMONG CAUSAL FACTORS

An additional and very important complicating factor is that many of the factors affecting cancer incidence interact additively or more than additively (synergistically). In addition, some may also act antagonistically. For example, Dr. Robert Squire (Johns Hopkins University) made the following summary statement:

"Numerous experiments involving cocarcinogenesis indicate that different carcinogens may have additive, synergistic, or antagonistic effects in organisms exposed to them. It is unlikely that we can predict which, if any, of the above effects will occur in the case of specific chemicals without observing their action experimentally, but numerous studies do demonstrate the existence of potential hazards." (Squire, S. 5)

A number of witnesses referred to the studies of Dr. Irving Selikoff (Mount Sinai School of Medicine), which showed the very marked synergism between cigarette smoking and asbestos in the induction of lung cancer:

"Evidence of the carcinogenic potential of asbestos was provided over the period 1935–1965 for a number of neoplasms, including bronchogenic carcinoma [1–3], pleural and peritoneal mesothelioma [4–6], and gastrointestinal cancer [7]. It was found in 1967, however, that for the most important of these neoplasms—lung cancer—the risk did not depend on asbestos alone. Rather, if there were not concordance of two agents—cigarette smoking and asbestos—the tumor was uncommon [8].

"In 1963, prospective observation was begun of 370 long-exposed asbestos workers in the New York metropolitan area. By April 30, 1967, no death from lung cancer had occurred among the 87 men with no history of cigarette smoking, despite their many years of occupational exposure to asbestos. In contrast, 24 deaths from lung cancer occurred among the 283 men with a history of cigarette smoking [8], although only 2.98 such deaths had been expected, given their smoking habits [9]. We suggested that the combination of the two factors—asbestos greatly increasing the lung cancer risk of cigarette smoking—had a sharp, multiplying effect. It was calculated that an asbestos worker who smokes cigarettes has eight times the risk compared to smokers of the same age who do not work with asbestos, and 92 times the risk of men who neither work with asbestos nor smoke cigarettes [8].

"These findings were based on limited observations, especially with regard to nonsmokers. Additional investigations confirm the original conclusions [10].

"The survivors of the original group of 370 men were followed to December 31, 1973. Altogether, 191 died from 1963 to 1973.

Among the 87 men with no history of cigarette smoking, two deaths (of 41) occurred from lung cancer; both men smoked pipes or cigars. Among the 283 with a history of regular cigarette smoking, there were 150 deaths, 45 of lung cancer [Table 1].

"A second, much larger, study was undertaken to investigate whether asbestos exposure without cigarette smoking truly did not increase the risk of lung cancer significantly, especially since such exposure was clearly associated with increased cancer risk at other sites (e.g., peritoneum, gastrointestinal tract) in nonsmokers. On January 1, 1967, we registered the entire membership of the insulation workers' union in the United States and Canada and have observed the group since. When the cohort was enrolled, each man was asked to record his lifetime smoking habits. Of those enrolled, 9,590 indicated that they were either then smoking cigarettes or had previously smoked regularly; 609 had a history of smoking pipes and/or cigars but no cigarettes; and 1,457 had never smoked regularly at all. Smoking habits were not recorded for 6,144 men. Analysis of lung cancer deaths among the 17,800 men to December 31, 1972, showed that increased risk of this neoplasm was limited to asbestos workers who also had a history of cigarette smoking. Among the 9,590 cigarette smokers, there were 179 deaths from lung cancer (of 640 all told); of the 2,066 men with no history of cigarette smoking, only 2 (of 93 total) died of lung cancer (Table 2). Unfortunately, data are not yet available detailing lung cancer risk specifically for amount and nature of smoking, as were available through 1965 [9]. Nevertheless, using the earlier tabulations, these new findings again demonstrate that asbestos workers who do not smoke, or smoke only pipes and/or cigars, have about the same lung cancer risk as men not occupationally exposed to asbestos dust. However, exposure to asbestos dust greatly increases the lung cancer risk among cigarette smokers [11].

"There is evidence [12] that uranium mining and cigarette smoking also interact as multiple factors. Moreover, an association between smoking and radiation has been noted [13] among Hiroshima and Nagasaki atomic-bomb survivors, with lung cancer disproportionately increased among the radiation-exposed individuals who also had a history of cigarette smoking." (Selikoff and Hammond, 1975, pp. 467–470; Exhibit to Squire Statement)

During his oral testimony, Dr. Selikoff (Mount Sinai School of Medicine) described the results from his most recent study:

"We found that among the 2,066 non-cigarette smokers there should have been 1.82 deaths, the way the statisticians put it, 1.82 deaths of lung cancer. There were eight. In other words, somewhere around four to five times as many. But this is certainly not a major public health problem. You had four times or five times the number of a very small number; and five times nothing is still not very much.

"On the other hand, you had again five times the already high risk of cigarette smoking, so that instead of 67 deaths anticipated, 325 actually occurred, confirming not simply the carcinogenicity of asbestos in terms of lung cancer among those exposed, but also the extraordinary multiple factor etiology." (Selikoff, Tr. 1702)

Dr. William Nicholson (Mount Sinai School of Medicine) also commented upon the multiplicative effects resulting from exposure to asbestos and cigarette smoking:

"Increasing evidence is accumulating that many cancers have a multiple-factor etiology. For example, lung cancer in asbestos workers is strongly associated with cigarette smoking. In the large cohort of 17,800 insulators observed by Selikoff and Hammond, the smoking habits of the majority of workers were obtained at the beginning of their study. Table 8 illustrates the effects of cigarette smoking on lung cancer mortality. In 2,066 noncigarette smokers, only two lung cancers were seen in a six-year period; 179 were observed in 9,590 men with a history of cigarette smoking. Although the data are still insufficient to accurately determine the risk of dying of lung cancer in nonsmoking asbestos insulators, they do suffice to establish that the risk is less than that for cigarette smoking males in the general population who do not work with asbestos. However the combination of cigarette smoking and asbestos has a multiplying effect. From data on the New York and New Jersey insulators cohort, it has been calculated that the combined risk for dying of lung cancer of an asbestos worker who smokes is 92 times that of an individual who neither smokes nor works with asbestos.

"It is clear that it would be necessary to include evaluation of multiple-factor effects in calculating threshold values for asbestos cancer risk. It is equally clear that this requirement would introduce insurmountable sample-size, statistical, and sampling requirements." (Nicholson, 1976, p. 164; Exhibit 11 to Nicholson Statement) (footnote omitted)

Dr. David Kaufman (Univ. of N. Carolina) described his experimental work on interactions between ferric oxide and benzo(a)pyrene (BP) in causing lung cancer in hamsters and concluded:

"The first major issue that was considered was the effects of two or more carcinogens, specifically how their interactions may have a greater effect than that of any of the individual constituents. Our work shows that treatment of experimental animals with two carcinogens given sequentially can result in an increase in tumor incidence and a decrease in time necessary for the appearance of tumors of the respiratory tract. In accord with our findings, the several cited examples of work by others show that in an analogous manner combinations of carcinogens can produce tumor incidences greater than that expected with either of the single treatments or that anticipated as the sum of the effects of the single treatments. The examples cited indicate that this type of interaction can be demonstrated in tissues other than the respiratory tract and in experimental animals other than the hamster as well as in *in vitro* studies. Furthermore, I have cited examples where combinations of carcinogen exposures in humans also produces a greater than an apparent additive tumor response."

"A second major point that was indicated was that carcinogen exposures may be potentiated by a variety of non-carcinogenic factors. Our work shows that the association of benzo(*a*)pyrene with a non-carcinogen, Fe_2O_3, specifically when the BP is adsorbed to the Fe_2O_3, greatly enhances the resultant tumorigenic effect of the BP dose. Our results suggest that at least in part this effect may [be] related to the prolonged retention of the BP within the respiratory tract when attached to the Fe_2O_3 particles. Our illustrations of the experimental work of others indicate that such diverse treatments such as inhalation of SO_2, performance of a partial hepatic resection, feeding of phenobarbital, or application of croton oil or its active constituents, all of which are not by themselves carcinogenic, may all increase the incidence of observed tumors and/or reduce the time needed for the apearance of the tumors". (Kaufman, S. 19)

Indeed, a committee reporting to the Director of the National Cancer Institute in 1973 advised him that synergistic effects are likely to be of overwhelming importance in the induction of human cancer:

"Of major importance in this connection is the fact that the carcinogenic process initiated by a submanifestational dose of one agent may be brought to completion by a submanifestational dose of another agent of entirely different chemical structure, even when exposure to the first agent has ceased and even when long periods of time intervene between the two types of exposure. It appears that carcinogenesis can result from the summation of a number of irreversible alterations in cells, no one of which may suffice to produce a manifest cancer. This is known to be true of the carcinogenic effects of ionizing radiation; it is the total lifetime exposure that is the determining factor. Similarly, there is no evidence that a newborn animal exposed to a chemical carcinogen ever reverts to normal with respect to the likelihood of developing cancer. On the contrary, throughout its lifetime it has a higher risk of developing cancers than its untreated littermates.

"Under natural conditions, few if any people are exposed to a single pure chemical. Such exposure is usually to mixtures and crude products. Isolation of individual carcinogens is often complicated by the presence of other chemicals that can enhance or retard the carcinogenic reaction. For example, the role of such cocarcinogens and/or anticarcinogens in tobacco smoke may be as important as that of the several carcinogens that have been isolated in minute quantities.

"There can be no doubt that the general population is continually exposed to hundreds of chemical, physical and biological agents that produce cancers of various types in various species under certain conditions. Little is known about interactions between

several of these agents, but there is clear evidence that such interactions do exist. Additional complexities are introduced by evidence of involvement of intestinal bacteria in metabolic conversions of the active carcinogen in cycad meal.

"In view of the enormous and largely unpredictable differences in susceptibility of different species and different individuals to most carcinogens, and the fact that the significant factor is the totality of lifetime exposure (which can never be estimated accurately) to a large number and variety of carcinogenic agents and cocarcinogens, some known and many unknown, little if any useful practical purpose can be served by attempts to assess the hazard for man of a particular environmental carcinogen on the basis of quantitative data obtained in laboratory animals. Emphasis on this point not only is misguided but is misleading and may be harmful." (NCI Ad Hoc Committee, 1973, p. 11; Hearing Exhibit 24)

Several expert committees have also noted the potential for synergistic interactions. A Committee of the National Academy of Sciences stated in *Drinking Water and Health:*

"Some experience in man begins to give answers to these questions. The few known interactive effects in man are related to exposure to cigarette smoking combined with some other exposure—industrial or social. These are the combined effects of: cigarette smoking (inhaled); asbestos exposure (Selikoff, 1968); inhalation of radon, as in the case of the uranium miners (Lundin, 1971); and the use of alcohol (Rothman, 1972). All of these show risks that are more than additive. For example, the heavy smoker has about two times the risk of the nonsmoker of dying of cancer of the oral cavity. The heavy drinker-heavy smoker has about 15 times the risk of the nonsmoker, nondrinker. Reports from Great Britain support the idea that the recent reduction in male lung cancer mortality, particularly in Greater London, with small changes in cigarette smoking and large changes in air pollution have come about through an interaction between urban air pollution and cigarette smoking (Lawther, 1976)." (NAS, 1977a, p. 50; Appendix I to Rall Statement)

In their report to the Surgeon General, the Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens also addressed this problem:

"Interactions among multiple factors have received limited attention to date. There are well-documented instances in animal studies of strong synergistic effects produced by chemicals in combination with radiation, viruses, or other chemicals. The epidemiological patterns of certain human cancers implicate combined effects of multiple agents (e.g. inhalation of radon and radon daughters in uranium mines and cigarette smoking)." (NCI Ad Hoc Committee, 1970, p. 4; Exhibit 10b to Epstein Statement)

The concept of *carcinogenesis* is complicated by the recognition that most cancers may have multiple causes and progress through multiple stages. Certainly it may be improper to attempt to assign every cancer to a single carcinogenic factor, as pointed out by Dr. Rall and Dr. Upton in the passages quoted above. One of the most complete and rigorous definitions of a *carcinogen* in the Record may be the one offered by Mr. Richard Peto (Oxford University), who defined a carcinogen as any external agent that directly or indirectly increases the likelihood that a transformed cell will pass through one of the stages in the process of development of cancer:

"Definitions

1. The incidence rate of cancer among people of age t, which may be written I(t), is the probability that a person of age t will develop a new cancer tomorrow.

2. Among cells which have suffered certain heritable changes and are at risk of suffering a particular further heritable change the event rate, R, of that further change is the probability that a cell which has been ready for such a change for some time, but hasn't yet suffered it, will do so tomorrow.

3. If we number the heritable changes suffered by a particular cell en route from normality to malignancy 1,2, . . . , n (where n might be, e.g., somewhere around 4 or 6), then we can call these changes stages, and we can call a cell that has suffered only the first two such changes a stage-II cell, and so on. A particular person might already contain several stage-I cells, some stage-II cells, and a few stage-III cells when the cell which eventually kills him suffers the first of its stages. Thus one cannot usefully say that a person has reached stage III, only that certain cells have done so. Confusion on this point is surprisingly common.

4. Let the event rate of the change into stage I be called R_1. In some multistage models R_i is constant, whereas in others it varies with age, or with the condition of the neighboring cells, or with the time since that cell suffered its previous change.

5. Any external agent that directly or indirectly increases any of the n event rates, $R_1 \ldots R_n$, may be called a carcinogen, [2] as may any agent which makes it more probable that a fully transformed cell will proliferate successfully rather than be eliminated or held in check." (Peto, 1977, pp. 1404–1405, Annex D to Peto Statement) (footnote omitted).

Mr. Peto added in a footnote:

"[2] Some authors use the word 'carcinogen' in a more limited sense and then refer to other agents, which I would also call carcinogens, as cocarcinogens, promoters, enhancers, etc. In this report, any agent, process, or habit that increases the risk of cancer among people of a particular age will be called a carcinogen whether or not it operates in one of the ways listed in definition 5." (*ibid.*, p. 1405)

OSHA generally concurs with the broad definition of the term *carcinogen* as used in the above passage, and notes that it includes agents referred to by others as "cocarcinogens, promoters, enhancers, etc." The NCAB Subcommittee on Environmental Carcinogenesis also recommended a broad definition of a "carcinogen", as follows:

". . . the term carcinogen is used in its broad sense, because in most of the current human epidemiologic approaches and certain animal bioassays it is not possible to differentiate clearly between initiating agents, and certain modifying factors. Any factor or combination of factors which increases the risk of cancer in humans is of concern regardless of its mechanism of action. (NCAB 1977, p. 461).

It is reasonable to discuss all such agents under the same heading, if only because of the practical impossibility of distinguishing between them experimentally.* Whether all such agents should be *regulated* alike is a more complex question, which will be discussed below.

D. DISTINCTIVE FEATURES OF CARCINOGENESIS

It is apparent from the testimony summarized above that carcinogenesis has a number of distinctive features which set it apart from other types of toxicity and require that it should be treated in a different way by regulatory agencies. Dr. Robert Squire (Johns Hopkins University) discussed this issue as follows:

"It is probably true that all substances are toxic at some level and that most are safe at another, since many metabolic, pharmacokinetic, and detoxification or repair processes are dose-dependent".

"Not all substances, however, are carcinogenic, including many that exhibit other types of toxicity and can cause death. In the current NCI carcinogenesis bioassays (reports in progress), over one-half of the substances tested showed no carcinogenic effects, although most were to some extent toxic at the levels tested. These results are particularly revealing, since the chemicals were selected for testing because some concern for their carcinogenic potential existed. Carcinogenicity is in fact a specific type of toxicity, resulting in a persistent and self-perpetuating alteration of cells, apparently through the interaction of the ultimate carcinogen and cellular genetic

* As an example of an alternative definition, Dr. William Butler (NACA) proposed the following: "A chemical carcinogen is a substance that causes a cell or group of normal cells which would not otherwise have shown this property, to change its biological behavior and demonstrate autonomous growth of a malignant character." (Butler, S. 17) Apart from the problem that this defines a carcinogen as the single cause of a multi-causal phenomenon, the reason given by Dr. Butler for rejecting OSHA's definition was because it was "purely operational" (S. 16). However, for regulatory purposes, OSHA believes that it is obviously necessary to use a definition that is operational. Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska) also discussed the definition of a carcinogen in OSHA's proposal, and commented that "definition is a enormously difficult, if not impossible, task" (S. 5, 7, 17).

material or other cellular macromolecules that control cellular differentiation (Miller 1977). It is perhaps identical to somatic mutation, a type of genetic toxicity, but it is to be distinguished from most other types of toxicity, which do not result in heritable cell alterations. The mechanisms of carcinogenicity are unknown, but the phenotypic expression of the carcinogenic process is clearly different from that of non-neoplastic toxicity.

"Thus, I believe that we are compelled to consider carcinogenesis a specific and perhaps unique toxic manifestation. We should not, in my view, regulate carcinogens as we do many other toxic substances". (Squire, S. 7–8)

Dr. Umberto Saffiotti (NCI) provided a recent, and very thorough, analysis of the differences between what he termed "terminal" and "self-replicating", e.g., carcinogenic, toxic effects:

"Traditional" toxicology has been concerned mostly with toxic effects having the following characteristics:

(1) They appear early; (2) the intensity of the induced pathology is directly correlated with the intensity of the toxic exposure; and (3) manifestations of toxicity are due to altered functional products, degenerative changes, or death of the target cells themselves. I refer to these as terminal toxic effects * * *

"The traditional approach for estimating an acceptable level for human exposure to agents inducing such terminal toxic effects has been that of using relatively short-term animal toxicity tests, determining a no-effect level under the conditions of test, and then applying a so-called safety factor for extrapolation to the human situation. If these estimations still turn out to be excessive for humans, as evidenced by the consequent development of toxic symptoms, then exposures can be further reduced until the symptoms disappear. This approach, of course, implies that the symptoms indicating toxicity should appear early and that the damage should be reversible. This traditional empirical approach to the setting of thresholds is well summarized in a statement I heard from a British colleague: "Find a no-effect level in animals, divide by 100, and pray."

"These traditional methods in toxicology are inadequate to deal with the pathogenetic mechanisms involved in the chemical induction of cancer. The characteristics toxicologic event in carcinogenesis is a trigger change in the target cell's regulatory mechanism, which determines a self-replicating cell lesion. The carcinogenic event so modifies the genomes and/or other molecular control mechanisms in the target cells that these are then able to give rise to a progeny of permanently altered cells. It is indeed this progeny of cells which represents the induced pathology. The expression of the toxic injury therefore does not derive from the same cells that were originally hit by the toxic agent, or from their functional products, but rather from the proliferation of a new population of altered cells.

"The subsequent growth of the altered cell population into a clinically detectable neoplasia follows the rules of biological determination. In this respect, carcinogenesis fits well, at the somatic-cell level, into the general pattern of biological evolution defined by Jacques Monod as a sequence of chance events followed by the necessity of biological determination of their expression (Monod 1970; Saffiotti 1977).

"The critical molecular injury caused by specific carcinogenic agents may be quantitatively extremely limited—even to a few cells—and may therefore remain 'silent.' What will make it manifest is the proliferation of the altered cell population, the extent of which is dependent on host conditions. The intensity of the pathological response in a subject, i.e., the growth rate and spread of a cancer, is not dependent on the level of carcinogenic exposure received by the subject. In fact, each tumor is characterized by independent progression (Foulds 1969).

"Carcinogenic effects are therefore intrinsically different from the terminal toxic effects described above. The characteristics of carcinogenic effects are the following: (1) Their appearance is delayed; (2) the frequency of the expression of injury (e.g., tumor incidence) in the exposed population is directly correlated with the intensity of the carcinogenic exposure, but the intensity of the induced pathology (e.g., tumor growth and spread) is independent of the intensity of the carcinogenic exposure; and (3) the manifestations of toxicity are due to the proliferative response of a new altered cell population. I refer to these effects as self-replicating toxic effects (Saffiotti 1977)". (Saffiotti, 1977a, pp. 1311–1312; Exhibit to Saffiotti Statement)

Dr. Marvin Schneiderman (NCI) and his colleagues also discussed the differences between carcinogenesis and other manifestations of toxicity:

"First, cancer appears often to be a disease of DNA damage or mis-repair, or incomplete repair and there is evidence that large numbers of molecules of an offending agent are not needed to cause DNA damage. Second, cancer is a progressive process. Once the last stage is started, the cells appear to develop an existence of their own, growing out of bounds as it were. The initiating agent doesn't need to be present any longer once the process has started on its way (although a 'promoter' may need to be around for a long time to produce high risks). Third, many agents seem to lead to the same cancer. This implies, that unlike bacterial disease where one agent leads to one disease we must not consider each agent in isolation, but we need to put the doses of these same end result materials together additively (at least)". (Schneiderman et al., 1978, p. 2; Appendix D to Schneiderman Post-Hearing Comments)

Dr. Richard Griesemer (NCI) made a similar point:

"The assumption that the 'principles of toxicology' apply to carcinogenesis has not been proved. In particular, the evidence that exposure of cells to very small amounts of carcinogens results in irreversible changes that can be shown to be the beginning of the carcinogenic process indicates that caution should be used in attempting to predict threshold levels until more data are obtained." (Griesemer, S. 7)

These and other exhibits in the proceeding emphasized four distinctive features of carcinogenesis: single-cell origin, irreversibility, age-dependence, and latency.

1. Single-cell origin

Several witnesses referred to evidence that cancers develop from foci of a very few cells, probably in many cases from a single transformed cell.

Dr. Hoel, Mr. Peto, and their colleagues discussed such evidence:

"Single-Cell Origin. If individual cancers arise from an original, single, "transformed" cell, then the statistical nature of the carcinogenic dose response will be governed by the extreme tail of the "transformation" response distribution. The effect of this is to make virtually any process of discrete events approximately linear at low dose. Two primary observations indicate the single-cell origin of cancers. In women who are heterozygous for electrophoretic variants of X-linked glucose-6-phosphate dehydrogenase, cancers are uniformly of one phenotype or the other (6), whereas a comparable amount of normal tissue is composed of a mixture of cells of the 2 phenotypic classes. Further evidence for the single-cell origin of cancers comes from experimental efforts in which "transformed" cells are transplanted into whole animals. Although there is much controversy associated with various aspects of this line of research, it seems that the ability of a single cell to give rise to a cancer is well demonstrated (7). Thus, 2 lines of evidence indicate that cancer can be most reasonably assumed to arise from events associated with or occurring inside single cells. (Crump et al., 1976, p. 2977 (citing Fiaklow, 1974 and Gartler, 1973); Annex C to Peto Statement)

Dr. Lorenzo Tomatis (IARC) also discussed this evidence in one of his exhibits:

"The capacity of single cells to give rise to cancer has been demonstrated in a series of experiments using single embryonal carcinoma cells (Kleinsmith & Pierce, 1964). The hypothesis of the single-cell origin of cancer is supported by the finding (see Fiaklow, 1972, for review; Smith et al., 1971) that cancers in women who are heterozygous for variants of the X-linked glucose-6-phosphate dehydrogenase are in many cases of a single phenotype, while comparable amounts of normal tissue are composed of a mixture of cells of the two phenotypic clones. A single clonal origin of cancer would be compatible either with tumour initiation resulting from a rare event such as a spontaneous somatic mutation, or with the presence of a very limited number of cells susceptible to a generalized oncogenic stimulus. A multiple clonal origin would imply that a large number of cells in the target organ are susceptible to the oncogenic stimulus or that the oncogenic stimulus was

very powerful. (Tomatis, 1977a, pp. 299–300; Appendix 3 to Tomatis Statement)

Dr. Emmanuel Farber (University of Toronto) introduced his own experimental studies which showed liver carcinomas developing from minute foci: these studies were interpreted in terms of a single-cell origin (Farber, 1978, p. 11, Appendix D to Farber Statement, referring to Friedrich-Freska and Hoffmann 1969, Schieferstein et al., 1974, Scherer and Hoffmann, 1971).

There is evidence that the first stage in initiation of carcinogenesis may result from the interaction of a molecule of the carcinogen with DNA or other genetic material in the cell (Cairns, 1977; Boutwell, 1974, 1977; Berenblum, 1974; Kotin, S. 17–18; Rall, S. 4; Hart, S. 7–14). Hence it would follow from the fact that cancer develops from a single cell, that cancer may be initiated by the interaction of a single molecule of a carcinogen with the critical target site in a cell (NAS, 1977a, p. 37–38) * This is not to say that a single molecule administered to the animal will suffice to ensure that it will develop cancer, since the probability of this interaction taking place appears to be dependent on dose. However, it does indicate that some tumors may be traced back to a single molecular interaction which began the progression leading to a transformed, self-replicating cell line. This is of profound importance for the concept of "threshold" doses. (See Section V. D. 10 below on Thresholds).

2. Irreversibility

A number of exhibits discussed the *irreversibility* of carcinogenic effects, and their distinction in this respect from other toxic effects. The Ad Hoc NCI Committee's report to the Surgeon General presented the matter as follows:

"The effects of carcinogens on tissues appear irreversible. Exposure to small doses of a carcinogen over a period of time results in a summation or potentiation of effect. The fundamental characteristic which distinguishes the carcinogenic effect from other toxic effects is that the tissues affected do not seem to return to their normal condition. This summation of effects in time and the long interval (latent period) which passes after tumor induction before the tumor becomes clinically manifest demonstrate that cancer can develop in man and in animals long after the causative agent has been in contact and disappeared." (NCI Ad Hoc Committee, 1970, p. 2; Exhibit 10b to Epstein Statement)

This concept was further elucidated at the hearing by Dr. Stewart (NIH), quoting from the unanimous 1973 report of an eight man committee, of which he was chairman, to the Director of NCI. The committee stated:

"Of major importance in this connection is the fact that the carcinogenic process initiated by a submanifestational dose of one agent may be brought to completion by a submanifestational dose of another agent of entirely different chemical structure, even when exposure to the first agent has ceased and even when long periods of time intervene between the two types of exposure. It appears that carcinogenesis can result from the summation of a number of irreversible alterations in cells, no one of which may suffice to produce a manifest cancer. This is known to be true of the carcinogenic effects of ionizing radiation; it is the total lifetime exposure that is the determining factor. Similarly, there is no evidence that a newborn animal exposed to a chemical carcinogen ever reverts to normal with respect to the likelihood of developing cancer. On the contrary, throughout its lifetime it has a higher risk of developing cancers than its untreated littermates." (NCI Ad Hoc Committee, 1973, p. 11; Hearing Exhibit 24)

The Safe Drinking Water Committee of the National Academy of Sciences also emphasized the irreversibility of carcinogenic processes:

"Some effects of toxic chemicals are unmistakably irreversible. They include terata, malignant tumors, mutations in offspring of exposed animals, and some neurological changes. These are gross manifestations of specific chemical-cell interactions, and it is possible or probable, that there are early reversible effects, either in the cellular process first affected or at intervening stages. Prediction of adverse effects from short-term studies is possible if the critical dose and the rate-limiting factors that determine reversibility are known. Without this knowledge, evaluation of toxicity will generally deal more with the possibility of irreversible effects than with speculatively reversible effects."

* * * * * *

"It is more prudent to treat some kinds of toxic effects that may be self-propagating or strictly cumulative, or both, as if there were no threshold and to estimate the upper limits of risk for any given exposure. Included among these are effects that result from an initial, chemically induced alteration in cellular genetics that is transmitted by cell propagation. Carcinogenesis and mutagenesis are examples in which a single cell transformation has the theoretical potential for irreversibility, which might involve self-propagation, even in the absence of further exposure." (NAS, 1977a, pp. 23, 25; Apendix I to Rall Statement)

Some witnesses interpreted certain evidence as possibly indicating reversibility. For example, Dr. Paul Kotin (Johns-Manville) cited the work of Dr. Farber (Univ. of Toronto) as evidence for the proposition that early lesions induced by carcinogens regress if exposure is terminated (Kotin, S. 19; Kotin, Tr. 8744). However, Dr. Farber's own papers showed that although the *Nodular lesions* may regress, foci of altered cells remain in latent form and can be selected to proliferate by appropriate stimuli up to 17 months later (Solt and Farber, 1976; Farber, 1978, p. 17, Appendix D to Farber Statement). Dr. Farber also commented as follows on Dr. Kotin's interpretation:

"As he [Dr. Kotin] correctly pointed out, early preneoplastic liver lesions do regress unless the environment is appropriate for continued stimulation of the initiated cells (promotion). However, we also pointed out that the induction of initiated cells was an irreversible phenomemon. As in the skin, these early lesions were found to persist for long periods (up to 44 weeks) and could be stimulated to proliferate at will by creating the appropriate environment for selection.

"Using our new assay for initiation, we have not found a dose of diethylnitrosamine that does not initiate if accompanied by cell death plus regeneration or better a round of cell replication. Thus, we cannot be certain that a threshold actually exists for initiation of carcinogenesis. This is particularly so, given the well known variation in susceptibility to carcinogens of animals of different genetic backgrounds." (Farber, Post-hearing Comment. p. 1)

In the context of the multistage models of cancer, "irreversibility" does not mean that a transformed cell will inevitably develop into cancer. It means that the transformed cells will retain their *potential* to progress through later stages into fully-developed cancer for most or all of the lifetime of the animal. This progression is dependant upon other environmental or host factors which trigger subsequent transformations or select for growth of the transformed cell line. As Dr. Farber pointed out (Farber, 1978, p. 18; Appendix D to Farber Statement), the number of cancers that appear in experimental rats 12 to 18 months after exposure is "many magnitudes" smaller than the number of foci of transformed cells that can be detected early. Thus only a very small fraction of the transformed cells eventually progress to cancers, and these do so only in circumstances favorable for such progression. However, there is no evidence in this or other studies* that

* A number of witnesses disagreed with this point: see, for example, Dr. Roe (S. 49, 58), and Dr. Kotin (S. 11).

* Dr. Francis Roe (AIHC) cited evidence that the initiating effects of carcinogens on mouse skin declined in magnitude over periods of 24–52 weeks after exposure. OSHA does not find these studies (Roe et al., 1972, Berenblum and Shubik, 1949, Roe and Salaman, 1954) to be compelling evidence for reversibility, because the experiments did not exclude other explanations for the dependence of tumor yield on age. Even if they were taken at face value, however, they appear to show effects of an initiating dose persisting for up to half the lifetime of the animals.

the initial transformations can be reversed: indeed, they remain latent for most or all of the animal's lifetime (*id.*). The importance of these findings for regulation of carcinogens is that even brief exposures early in life must be assumed to have irreversible effects which may be manifested as cancers late in life. If a person has been exposed to a carcinogen that affects an early stage in cancer development, the only way to avert the consequences of this exposure would be to eliminate subsequent exposure to agents required for late stages. Since these are often unknown and may be non-specific, the practical consequence is that early exposure irreversibly increases the probability of developing cancer.

An important consequence of the irreversibility of carcinogenic transformations is that humans exposed to a carcinogen generally remain at increased risk of developing cancer even after exposure to the carcinogen has ceased. Empirical studies of this effect in rodents have been discussed in preceding paragraphs. Two exhibits in the Record reviewed evidence for the persistence of risk in humans, derived from epidemiological studies of exposed groups. Both Peto (1977, pp. 1415–1418) and the NCI, NIEHS and NIOSH Institutes' Report (Appendix A) discussed data on lung cancer in cigarette smokers. Persons who continue to smoke show an incidence of lung cancer which increases rapidly with age (approximately as the fourth power of age); their relative risk to that of non-smokers remains roughly constant with age. Persons who stop smoking remain at increased risk, but their cancer incidence does not continue to increase as fast as that of continuing smokers; instead it approaches (but never falls as low as) that of non-smokers after 20 or more years. Both Mr. Peto and the NCI, NIEHS and NIOSH Institutes' Report interpreted these data as indicating that cigarette smoke affects the penultimate stage in the multi-stage process.

"The incidence rate of cancer is the number of cells that have suffered all but the final stage times the event rate for the final stage (times the probability that a fully transformed cell will escape control). If, therefore, we suddenly change the event rate for the final stage, a sudden change in the inception rate of cancers will result, which will (after allowing for the time they take to grow visible) quickly affect the incidence rate.

"This is not what is observed among regular smokers who give up smoking; the extra incidence rate stays approximately constant after smoking ceases.

"This is one of the strongest, and hence most useful, observational restrictions on the formulation of multistage models for lung cancer. It was suggested by Pike, who also analyzed the first 17 years of Doll's data on British doctors to demonstrate that these data were compatible with it (Doll 1971). I have recently analyzed the full 20 years of Doll's data, and I find that if we take Doll's data plus the data of Dorn (Kahn 1966) and of Hammond (1966), the same pattern emerges. Hammond's (1966) impression that lung cancer incidence rates revert to nonsmoker incidence rates 10 years after stopping appears to be wrong, perhaps due to an artifact of chance. The truth seems to be that when smokers quit, their extra lung cancer incidence rate remains remarkably constant for at least 15 years thereafter, and probably for longer.

"This is still good for the individual—the large increases in the lung cancer incidence rate that would have occurred later had smoking continued are avoided.

"If a simple multistage model is accepted, with smoking increasing the event rate of the penultimate stage, this constancy of extra annual incidence after smoking has been stopped is what would be expected, and in any model it suggests that smoking cannot possibly be acting on the final stage. If a model in which partially altered cells have a selective advantage is posited, then this selective advantage must cease when smoking ends; otherwise, the number of cells ready to undergo the last stage would increase and so would the extra lung cancer incidence rate attributable to past smoking. In other words, if proliferation of partially altered cells occurs and affects the kinetics of lung cancer induction, then encouragement of this proliferation must be the way, or one of the ways, in which smoking increases the risk of cancer. (Peto, 1977, p. 1415, citing Doll, 1971, Kahn, 1966, and Hammond, 1966; Annex D to Peto Statement)

* * * * *

"For cigarette smoking, the incidence of lung cancer increases with the daily amount smoked (either linearly or perhaps quadratically) and with the fourth power of duration of smoking, for current smokers. On stopping smoking the incidence does not further increase, but remains approximately constant with age until it approaches that of non-smokers after some 20 years (Doll and Peto 1976). The relative risk therefore falls within five years of stopping smoking, as shown in Figure 1a" (NCI, NIEHS and NIOSH Institutes' Report, 1978, p. A–1; Hearing Exhibit 224b) (Footnote omitted)

On the other hand, data for persons exposed to three other carcinogens (radiation, asbestos, and nickel) indicate no such decline in relative risks even 35 years after exposure. Instead, the incidence of the induced cancers continued to rise with age in the way observed in continuing smokers. This is what is expected in a multistage process if the carcinogen affects one of the earliest stages, and the factors influencing subsequent stages remain unchanged:

"For radiation, leukemia behaves differently from tumors of epithelial origin. Following a single course of radiation treatment for ankylosing spondylitis (Smith and Doll 1978), the relative risk for leukemia rises rapidly, reaching a peak within 3–5 years, then decreases to become inappreciable some 12–15 years after exposure (Figure 1b). The relative risks for epithelial tumors of heavily exposed organs, however, remain low until 10 years after exposure, then rise and remain on a plateau for the remainder of the observation period (Figure 1c).

"Other epidemiological data on risks from irradiation show similar behavior for leukemia (A-bomb survivors) and for breast cancer (A-bomb survivors, women given radiation treatment for tuberculosis or post-partum mastitis).

"The two examples just given provide the two extreme possibilities, continually elevated risk following exposure of very limited duration, or a rapid fall in risk following cessation of a long lasting exposure.

"Asbestos and nickel provide two examples of occupational exposures where cohorts have been followed over an extended period of time. Asbestos causes lung cancer, cancer of the gastrointestinal tract, and mesotheliomas (Selikoff and Hammond, 1978). Among a cohort more than two thirds of whom had been exposed for less than two years (Newhouse and Berry, 1976), the incidence of mesotheliomas increased with increasing rapidity until the limit of the observation period, 35 years after first exposure (Figure 1d). Conversion of these incidence figures into corresponding values for relative risk is not helpful due to the rarity of the non-occupationally related disease. However, the absolute risk, as given by the incidence figure, shows no sign of leveling off even thirty years after cessation of external exposure. Extrapolation of the incidence curve to higher age groups would seem justified, to give an estimate of 8–10% of deaths due to mesothelioma predicted in the group under study (Newhouse and Berry 1976).

"For cancer of the lung the data have not been presented in such clear fashion, but all studies indicate an increase in relative risk for the period more than twenty years after start of exposure compared to 10–19 years after start of exposure. Assumption of a constant relative risk would appear to be conservative (Selikoff and Hammond 1978; Peto et al. 1977; Newhouse and Berry 1976; Knox et al. 1968).

"For nickel, the main carcinogenic hazard for the cohort from Wales appears to have been removed from the environment around 1930 (Doll, Matthews and Morgan 1977). Nevertheless, there has been no indication that the relative risk for either lung cancer or for cancer of the nasal sinuses has fallen over the decades following the reduction in hazard (Doll et al. 1970, 1977) up to the most recently reported follow-up ending in 1971. Similarly in the Norwegian study (Pedersen 1973), the great reduction in exposure to dust and fumes since 1950 is not reflected in any reduction in relative risk. Interestingly, the values for the relative risk (average over follow-up to 1971 in both cases) for the Welsh cohorts exposed before 1930 and the Norwegian cohort exposed before 1950 were similar, approximately 10-fold.

"One would conclude from these two examples of occupational exposure that the epithelial tumors induced behave more like epithelial tumors related to radiation than to those related to cigarette smoking. Exposure to the aromatic amines would seem similar with risk among the exposed not falling two [decades] after removal from the workplace of the known carcinogens, but in this situation the replacements for the carcinogens may themselves have been carcinogenic (Fox and Collier 1976).

"The different types of behavior described above can be [derived] from the widely accepted multi-stage theory of carcinogenesis, wherein a cancer is assumed to arise from a single cell which then passes through a series of stages, the last of which leads irreversibly to a clinically apparent tumor. With k stages, and with probabilities of transition constant over age, one would predict the age-specific incidence to increase with age to the (k–1) power, as is observed for most epithelial tumors with k–5 or 6 (Whittemore 1977; Cook, Doll and Fellingham 1969)." (NCI, NIEHS and NIOSH Institutes' Report, 1978, pp. A–1—A–4; Hearing Exhibit 224b)

In conjunction with the experimental data from exposed animals, these epidemiologic data indicate that persons exposed to carcinogens, even for short periods, will remain at increased risk for most or all of their lives (see Dr. Shubik, (Eppley Institute, Univ. of Nebraska), S. 31). If the carcinogen affects a late stage of cancer development, the relative risk (though not necessarily the absolute risk) may decline quite rapidly after cessation of exposure, as in the case of cigarette smoking. On the other hand, if the carcinogen affects an early stage, the relative risks will remain high, as in the case of asbestos and nickel. If a worker is exposed to several carcinogens sequentially in the course of his working life, the relative risks may therefore be additive or multiplicative. These facts underline the importance of avoiding or reducing exposures to carcinogens if occupational cancer is to be prevented or reduced.

3. Age-Dependence

Numerous witnesses pointed out that the incidences of most cancers are strongly age-dependent. Basic data on age-specific incidence and mortality from various types of cancer were presented in several exhibits (American Cancer Society, 1978; Mason, *et al.*, 1975, 1976; NCI, 1975; Devesa and Silverman, 1978). Mr. Peto (Peto, 1977, pp. 1404–1409) pointed out that the incidence of most human cancers increases with the fourth, fifth, or sixth power of age, and that these patterns can easily be understood in terms of multi-stage models:

". . . multistage models give a very natural explanation for cancer being a hundred times rarer among young adults than among the elderly, but no plausible explanation has yet been offered for the fact that the risk of cancer in old age is not vastly different in species with very different life-spans.

* * * * * *

"Human incidence data suggest that if an inbred population of humans were to be exposed throughout life to constant levels of the types of environmental insults we now suffer, the separate incidence rates of all carcinomas in group 2 (other epithelial cells) (with the possible exceptions of the liver, which exhibits a mode in countries where liver cancer is very common, and nasopharynx, which is slightly more common among children than it ought to be) would each increase as the fourth, fifth, or sixth power of age up to at least age 75, in conformity with the predictions from several multistage models.*" (Peto, 1977, pp. 1404, 1409; Annex D to Peto Statement)

This dependence of cancer incidence on the 4th, 5th, or 6th power of age is often taken as evidence that cancer progresses through 3, 4, or 5 stages (NCI NIEHS and NIOSH Institutes' Report, 1978, p. A–4), but as Mr. Peto pointed out (Peto, 1977, p. 1407), this conclusion does not necessarily follow.*

Several witnesses discussed the relationships between cancer and aging. Dr. Francis J. C. Roe (AIHC) suggested that cancer is a disease of old age because natural selection would be expected to have led to the evolution of defense mechanisms that operate early in life:

"If there were a genetically determined susceptibility to develop cancer *early* in life, one would expect it to be 'bred out' of the species, since unaffected individuals would have a reproductive advantage over those affected. But there would be no tendency for a susceptibility to develop cancer *late* in life to be bred out. This may account for the fact that cancer is by and large a disease of the later or post-reproductive period of life." (Roe, S. 18, quoting Roe 1966a)

Similar comments were made by Dr. Farber (Farber, pp. 26–27, 1978; Appendix D to Farber Statement), and Mr. Peto (1977, pp. 1412–1414). Dr. Roe went further and suggested that cancer is of positive benefit to the species:

"Cancer in its many forms is undoubtedly a natural disease. It is probably one of Nature's many ways of eliminating sexually effete individuals who would otherwise, in Nature's view, compete for available food resources without advantage to the species as a whole." (Roe, S. 94)

OSHA does not subscribe to this viewpoint. In the first place it is based on a fundamental misunderstanding of the process of natural selection, which acts at the level of the individual and not at the level of the species. Apart from this, it does not accord with the existence of the elaborate defense mechanisms described by Dr. Roe and others, which operate even in the "sexually effete". Moreover, Mr. Peto (Peto, 1977, pp. 1412–1413) pointed out that most common human cancers are geographically variable and associated with recent changes in human life-styles. This suggests that they are not under the control of natural factors that are included in Dr. Roe's concept of "Nature's view". Indeed, it suggests that Dr. Roe was at least partly wrong in concluding that the common forms of cancer constitute a "natural disease".

4. Latent period

The fourth distinctive characteristic of cancer, the long *latent periods* between exposure and effect, was abundantly documented in the Record. Many witnesses pointed out that there is a long latent period between the initial events in carcinogenesis and the clinical manifestations of the disease: in animals this period extends up to a full lifetime and in humans there are instances of latent periods in the range 5-40 years. (Lijinsky, S. 24; Holmberg, S. 5; Millar, Appendix C, pp. 6–8; Stewart, S. 2; NCI Ad Hoc Committee, 1970, p. 2; Cole and Goldman, 1975, pp. 172–176; Selikoff, Tr. 1697–1722; Nicholson, Tr. 1711; Harris, Tr. 1991). Although several witnesses pointed out that latent periods are difficult to define or to measure precisely, there was no dispute that for many carcinogenic processes there is no visible manifestation of the effects of the initiating event for periods which may extend up to half a lifetime or more. For example, see Exhibit 186 B, p. 15 and p. 20 (P.H.C. of Bethlehem Steel Corp.). The consequences of this fact in complicating the identification of carcinogens are discussed below. For the general purposes of this Part, the most important point is that the regulation of carcinogens must be anticipatory in nature: it is not justifiable to wait until manifestations of toxicity are observed, because by then a whole generation of workers may have been exposed.

In case histories of human exposure to chemical carcinogens whose effects are characterized in this way by long latent periods, such as cigarette smoke or asbestos, conclusive epidemiological findings were not available until 20 or more years after the start of exposure, by which time large numbers of persons

*Several witnesses appeared confused between the concepts of multi-stage and "multi-hit" concepts of carcinogenesis (Chase, Tr. 8636–8637; Roe, S. 48–49). There is little evidence from epidemiology for multi-hit phenomena, which would result in much steeper dose-response curves than are observed (Peto 1977, pp. 1405, 1422). See also Schneiderman *et al.*, (1978; exhibit D to Schneiderman Post-Hearing Comment) for further discussion of this point.

had been exposed and a substantial cancer epidemic had been caused. Thus, as pointed out below, the significance of the long latent period for chemical carcinogenesis is that *it is impractical and imprudent to wait for results of epidemiological studies in humans;* prevention of chemical carcinogenesis in humans requires identification of the carcinogens by experimentation in laboratory animals with a short lifetime and a correspondingly short latent period for tumor induction. As the "expert" NCI Ad Hoc Committee's report to the Surgeon General stated:

"It is, therefore, important to realize that incidences of cancer in man today reflect exposure of 15 or more years ago; similarly, any increase of carcinogenic contaminants in man's environment today will reveal its carcinogenic effect some 15 or more years from now. For this reason, it is urgent that every effort be made to detect and control sources of carcinogenic contamination of the environment well before damaging effects become evident in man. * * * Environmental cancer remains one of the major disease problems of modern man." (NCI Ad Hoc Committee, 1970, p. 2; Exhibit 10b to Epstein Statement)

And, as Administrator Russell Train of EPA pointed out in *In Re Velsicol, supra:*

". . . the latency periods for cancer inducing chemicals tend to be long (in the tens of years), so that what results there are from the study of human exposure are difficult to gather and may well appear too late to save people from an already widespread chemical to which they are unavoidably exposed." (41 FR 7575)

E. CANCER AS AN ENVIRONMENTAL DISEASE

A number of participants cited evidence that cancer is an environmental disease, in the sense that many forms of cancer are strongly associated with environmental factors (*sensu lato*). Estimates that as many as 60–90 percent of cancers are associated with environmental factors were introduced into the record. For example, Dr. Arthur Upton (Director, NCI) summarized the evidence as follows:

"It is now widely recognized that the incidence of many types of cancer in the human population can be associated with a number of different environmental factors. The evidence for such statements is of several kinds:

1. International and national statistics on cancer mortality and incidence show enormous variations in the frequency of various types of cancer from country to country and even from place to place within a single country. In extreme cases, differences in cancer incidence between high-risk areas and low-risk areas are greater than 50-fold. Certain types of cancer are strongly characteristic of limited areas in the world.

2. Studies of migrants—i.e., persons who change their environment—show that their pattern of cancer incidence frequently changes from that of their country of origin to that of their country of adoption, although the change may not be complete within one generation.

3. Epidemiological studies have shown that many types of cancer can be associated statistically with a variety of environmental factors, including smoking, occupation, sunlight, dietary patterns, ionizing radiation, and exposure to drugs and other chemicals.

4. For a number of specific agents, including ionizing radiation and at least 20 chemicals, there is now good evidence that they cause cancer in humans. Their identification has been primarily by means of retrospective epidemiological studies of persons highly exposed to these agents, either in the workplace or in the course of therapeutic treatments with drugs or radiation." (Upton, S. 2–3)

Dr. David Rall (Director, NIEHS) summarized the findings as follows:

"It is generally recognized nowadays that cancer is an "environmental disease," in the sense that the incidence of cancer shows wide geographic variations and can be correlated with such variables as race, life-style, and exposure to radiation and chemicals. Estimates ranging up to 90% have been given for the proportion of cancers that can be associated with environmental factors in this broad sense." (Rall, S. 2)

Dr. Bo Holmberg (Swedish NBOSH) also discussed the evidence associating human cancer with environmental factors:

"*Cancer as an environmental disease.* Cancer consists of a number of diseases which are not evenly distributed between sexes, geographical areas, or occupational groups. Colon cancer, for example, is less common among Japanese than among west coast Americans. After moving into the United States, Japanese immigrants and especially their descendants tend to adopt a more "American" cancer pattern in this respect (Cairns, 1975). Skin cancer is more common in southern parts of Europe than in northern parts, and skin melanomas are more common in southern Sweden than in the north (*Cancer Incidence in Sweden (1971).*) Regional differences in incidence may also be found for other cancer sites; thus stomach cancer is more common in northern Sweden than in the south. When analyzing cancer incidence on a geographic micro-scale, one can also observe an urban-rural gradient for lung cancers. In addition, lung cancer and cancer of the urinary bladder are more common among men than among women. The most important carcinogenic factor responsible for the urban-rural gradient and the male/female difference in lung cancer incidence is tobacco smoking. A proportion of lung cancers, i.e., 5–10 cases per 100,000 per year, may be induced by general air pollutants possibly in combination with tobacco smoking (Karolinska Institute, 1978). Some occupationally exposed groups are also recognized as high risk groups for specific cancers when compared to other professions or when compared to the general population.

"When looking at cancer incidences in industrial countries, for example USA (Cairns, 1975), England and Wales (Higgins, 1974) or Sweden (Ericsson and Ringertz, 1972: Appendix 4), the incidence of some cancers has been increasing during the last decades. Looking for instance at cancer incidences in 1988 in Sweden (Ericsson and Ringertz, 1972) compared to those in the year 1959 (Fig. 1) one can observe an increase in age-adjusted incidence for many sites. This increase ranged from 10 to almost 100 percent during the 10-year period. For two types [of] cancer, stomach cancer and nasal cancer, the Swedish cancer incidences decreased during the same time period. Looking at absolute figures for incidence of all cancers, 19,000 new cases were reported in the year 1958 and 29,000 in 1971. The Swedish figures quoted are cancer morbidity data, not mortality data. During a 10 year period mortality figures may be changed by improvements in diagnosis and therapy. Morbidity figures provide a better measure of trends in the induction of cancer.

"Taken together, the patterns and trends in cancer incidences in various parts of the world indicate that cancer diseases are mainly due to environmental factors (Higginson, 1976). The increase in cancer incidences during such a short time period as 10 years (Fig. 1) cannot be explained by differences in life expectancy. Instead it must indicate that the exposure to causative environmental factors was markedly increased in the past, starting several years or a couple of decades ago and certainly prior to 1959. Only in a very few instances has it been possible to relate environmental cancers to exposures to specified single carcinogens. Cancer is more often due to multiple causes than to single causes." (Holmberg, S. 1–3)

Sir Richard Doll (Regius Professor of Medicine, Univ. of Oxford), in a paper cited by several participants in the OSHA proceedings, stated:

"Since Kennaway's seminal work, the evidence that cancer can be prevented has accumulated steadily and is now overwhelming. Whether it will ever be possible to prevent the disease altogether, as we can now prevent poliomyelitis and scurvy, is impossible to say until we know more about the mechanism by which it is produced; but we should be able to reduce the age-specific incidence rates—which account for a quarter of all deaths of men in Britain under 75 years of age—by at least 80 to 90%. That this is so, is suggested primarily by the great variation in the incidence of different types of cancer in different communities and in different parts of the world.

"This variation is illustrated in Tables 1 and 2, which show maximum and minimum incidence rates for all cancers that are common enough somewhere for the disease to affect more than 1% of men or women by 75 yr., in the absence of other causes of death. The range of variation is never less than fourfold and is sometimes more than a hundredfold." (Doll, 1977, p. 589; Annex E(a) to Peto Statement) (Footnotes omitted).

A number of other witnesses referred to similar estimates of the fraction of cancers attributable to environmental factors, citing original studies by Higginson (1969) and Boyland (1969), and a review by the World Health Organization (WHO Tech. Report Series 276, 1974). Very comprehensive reviews of the association between various cancers and environmental factors were introduced into the record in a number of different exhibits (e.g., Doll, 1977; Wynder and Gori, 1977; Weisburger, 1976). A book edited by J. F. Fraumeni, *Persons at High Risk of Cancer* (1975), included chapters devoted to reviews of associations between cancer incidence and such factors as occupation, diet, tobacco, alcohol, radiation, drugs, air pollution, sexual factors, and viruses.

A few witnesses expressed reservations about the reliability or applicability of estimates of the fraction of cancers attributable to environmental factors (e.g., Dr. Kessler, S. 2–5; Dr. Roe, S. 6–8). However, these witnesses were primarily concerned with emphasizing that "environmental" factors included such factors as life-style as well as chemical carcinogens, that genetic and other host factors could also be important, and that occupational factors comprise only one of the environmental factors. Neither the preamble to OSHA's proposal nor exhibits at the hearing suggested that cancer was caused *exclusively* by chemical carcinogens. OSHA accepts the broad conclusion presented by the witnesses quoted above, that the majority of human cancers are attributable to environmental factors, with the important proviso that most cancers have multiple causes and that some cancers may be caused by intrinsic as well as extrinsic factors. In the words of Dr. Rall (Director, NIEHS):

> "Recognizing that carcinogenesis is a multi-phased process whose progression is influenced by a number of factors, it makes little sense to assert that "only" 1–5% of cancers are attributable to a single factor. It would be consistent with our present knowledge to assert that *all* cancers are associated in one way or another with occupational factors, just as they are probably all associated with dietary factors, with genetic factors, and with hormonal factors." (Rall, S. 5)

Recognition by cancer specialists that many, if not most, human cancers are influenced by environmental factors is of extraordinary significance to OSHA—it means that occupational cancers may be preventable if the causative agents can be identified and human exposure to them eliminated or minimized. The opportunities for preventing cancer by reducing exposure to causative environmental factors were emphasized by many other witnesses, including Dr. Upton (Director, NCI) (S. 2–8), Dr. Richard Griesemer (NCI) (Tr. 971), Dr. David Rall (Director, NIEHS) (S. 5–6), Dr. Richard Bates (FDA/NIEHS) (S. 1–4), Mr. Paul Orrefice (Dow Chemical Co. (S. 7–8), Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska) (S. 1) and Dr. Robert Hoover (NCI) (S. 9–10).

F. MOST SUBSTANCES DO NOT APPEAR TO BE CARCINOGENIC

As studies are reported of the carcinogenicity of substances representing a wide range of molecular structures and used for a variety of purposes, there has been a tendency for some time to claim that all substances are capable of causing cancer if administered to experimental animals at sufficiently high doses. This claim appears to be based on the notion that carcinogenesis is a nonspecific kind of biological process associated with any substance under the right conditions, namely that test animals, bred for their sensitivity to carcinogens, when fed maximum tolerated doses of a substance for their lifetime become very ill and may be more susceptible to carcinogenic effects, either of the test substance or of other intrinsic or extrinsic agents or processes. For examples of this hypothesis, see the testimony of Dr. Roe (AIHC) and Dr. Olson. (St. Louis Univ.)

However, there is evidence that renders this claim very unlikely to be true. In fact, relatively few substances have been found to be carcinogenic and available evidence indicates that most substances do not cause cancer. A publication of the U.S. Department of Health, Education, and Welfare compiles and abstracts all substances tested for carcinogenic effects. ("Survey of Compounds Which Have Been Tested For Carcinogenic Activity," Volumes I–VII (1974–1976).) Although these volumes are not intended to provide a critical evaluation of the data on each of the substances, only about 17% of about 7,000 substances were reported as showing tumorigenic effects and this in spite of the fact that most of the compounds were selected for experimental study because of prior suspicion that they might show such effects (i.e., their structural similarities to known carcinogens). Thus, these data appear considerably to overstate the true proportion of carcinogenic substances in the human environment.

A critical review of the literature on carcinogenicity of chemicals has been undertaken by the International Agency for Research on Cancer (IARC) with the support and collaboration of NCI. Chemicals are selected for review in this ongoing program on the basis of two criteria: (a) that there is some evidence of human exposure, and (b) that there is some reason to suspect carcinogenic activity. Of 368 chemicals evaluated in volumes 1–16 of the IARC monographs, some evidence of carcinogenicity was found for 247.

Of these, some 26 substances have been identified as associated with excess cancer incidence in humans. Two hundred and twenty one showed some evidence of carcinogenicity from tests in animals, but these substances had not received adequate epidemiologic study to evaluate their effects in humans (Tomatis, *et al.*, 1978). In addition, fifteen occupational categories have been reported to be associated with excess cancer incidence without identification of a specific etiologic agent (NCI, NIEHS, and NIOSH Institutes' Report, 1978).

In a study sponsored by NCI from 1965 to 1968 and performed by the Bionetics Research Laboratories under contracts PH 43–64–57 and PH 43–67–735, approximately 140 pesticide and industrial chemicals were tested for carcinogenic activity. Pesticide chemicals, of course, are known to possess high biological activity as demonstrated by their use as pesticides. In addition, the substances tested in the Bionetics study were selected on the basis of a number of criteria, among which were: (1) published evidence of toxicity that suggested potential hazards to humans and (2) the similarity between possible test substances and substances of known carcinogenic activity. Each substance was fed to both sexes of two strains of mice at a maximum tolerated dose determined at a young age by continuous oral administration with both positive and negative controls for 18 months. Despite weighting in the choice of test substances, fewer than 10% of the substances tested definitely produced tumorigenic effects and most of the others gave no evidence of carcinogenicity (Innes *et al.*, 1969).

Furthermore, it has been recognized for many years that *negative* findings of carcinogenesis bioassays are often not published and are even rejected for publication (Report of the Panel on Carcinogenicity, Int. Union Against Cancer, "Carcinogenicity Testing," edited by I. Berenblum, IUAC, Geneva, 1969). Thus, the percentage of substances tested for carcinogenic activity and found positive may be even lower than present data indicate.

During the hearings to consider the intent of the Administrator of the U.S. Environmental Protection Agency to

cancel the registration of the pesticides aldrin and dieldrin, testimony was presented concerning this proposition. The Associate Director for Carcinogenesis of the Division of Cancer Cause and Prevention at NCI, Dr. Umberto Saffiotti, testified:

"Not all chemicals can cause cancers, contrary to some ill-informed belief: in fact, only a relatively small proportion of the chemical species that have been studied are capable of such activity. The activity is dependent on a number of specific chemical and physical properties of the molecules, which are gradually brought to light. It can be expected that, when thousands of new environmental chemicals will be tested, only a few hundred, or maybe just a few dozen, will be found to be carcinogenic, and it will be possible to concentrate our preventive measures on those." (Exhibit 40 of the EPA Public Hearings concerning the cancellation of the pesticide registrations of Aldrin and Dieldrin, 1973, pp. 7–8.)

Thus, the available evidence provides strong indication indeed that not all chemicals are capable of causing cancer and that only a small fraction of the total is so capable.*

Other federal regulatory agencies have made the same observations. In the DDT cancellation proceeding, In *Re Stevens Industries, et al.*, EPA IFR Docket No. 63 et al., 37 FR 13369 (1972), *aff'd EDF* v. *EPA*, 489 F. 2d 1247 (D.C. Cir. 1973), EPA Administrator William D. Ruckelshaus stated:

"The 'everything is cancerous' argument fails because it ignores the fact that not all chemicals fed to animals in equally concentrated doses have produced the same tumorigenic results." (37 FR 13371)

Likewise, in the Aldrin and Dieldrin suspension proceeding, *In Re Shell Chemical Co. et al.*, EPA FIFRA Docket No. 145, 39 FR 37265 (1974), *aff'd, EDF* v. *EPA*, 510 F. 2d 1292 (D.C. Cir. 1975), EPA Administrator Russell E. Train stated:

"Carcinogenicity is a relatively rare phenomenon exhibited by only a few of the many hundreds of thousands of chemicals." (39 FR 37268)

And in ordering the suspension of the pesticides Heptachlor and Chlordane in *In Re Velsicol Chemical Co. et al.*, EPA FIFRA Docket No. 384, 41 FR 7572 (1976), *aff'd, EDF* v. *EPA*, 548 F. 2d 998 (D.C. Cir. 1976), Administrator Train stated:

"Finally, I have noted some tendency, not entirely absent from the record, to assert that any chemical, if fed in sufficiently large amounts, will cause cancer in test animals. This is not true. A study sponsored by the National Cancer Institute tested 140 pesticides and industrial chemicals in two strains of mice, and less than ten percent of these were found to be carcinogenic." (41 FR 7575)

G. Occupational Factors in the Development of Cancer

1. In General

Almost all substances recognized as being carcinogenic in humans were first identified as such in the occupational setting. The reason for this is that workers are generally exposed to relatively high levels of chemicals and that clusters of unusual cancers among specific groups of workers can often be identified even without formal epidemiologic studies. As Dr. Irving Kessler (Johns Hopkins Univ.) pointed out (S. 9), even today relatively few adequate epidemiologic studies of exposed workers have been carried out, and much of the original evidence that occupational factors are associated with excess cancer risk was derived from case reports or descriptive surveys.

Several distinguished witnesses presented detailed evidence on specific chemicals and occupational situations associated with excess cancer risks. These witnesses included Dr. Robert Hoover (NCI), Drs. Irving Selikoff and William Nicholson (Mount Sinai School of Medicine), Dr. John Berg (Colorado Regional Cancer Center), Dr. David Wegman (Harvard Univ.), Dr. Bo Holmberg (Swedish NBOSH), Dr. David Schottenfeld (Cornell Univ.), Dr. Sidney Pell (DuPont), Dr. Irving Kessler (Johns Hopkins Univ.), Dr. Robert Morgan (Univ. of Toronto), Dr. Lorenzo Tomatis (IARC), and the panel from NIOSH comprised of Mr. Edward Baier, Dr. Richard Boggs, Dr. David Groth, Dr. Richard Niemeier, Dr. Robert Hill, Mr. James Gideon, Mr. Robert Schutz, Mr. Richard Waxweiler, Dr. Geoff Taylor, Dr. Ralph Yodaiken, and Mr. Howard Waldeman.

Among the many relevant exhibits introduced into the Record, four comprehensive reviews were particularly important: a symposium volume *Occupational Carcinogenesis* (Saffiotti and Wagoner, 1976), a review of Cole and Goldman, (1975), a survey in the NCI, NIEHS, and NIOSH Institutes' Report, (1978), and the *Monograph* Series of the International Agency for Research on Cancer.

According to these reviews and a paper of Tomatis *et al.*, (1978) summarizing the monographs of the IARC, some 18 industrial chemicals and/or industrial processes have been identified as associated with increased carcinogenic risks in workers. These occupational factors are the following:

Aflatoxins
4-Aminobiphenyl
Arsenic compounds
Asbestos
Auramine (manufacture)
Benzene
Benzidine
Bis(chloromethyl)ether
Cadmium using industries (? cadmium oxide)
Chloromethyl methyl ether
Chromium (chromate producing industries)
Haematite mining (perhaps due to radon gas)
Isopropyl oil
Mustard gas
2-Naphthylamine
Nickel (oxides)
Soot, tars, and oils
Vinyl chloride

(Tomatis *et al.* 1978, Table II)

In addition, excess cancer incidence has been reported in a number of other occupational groups without identification of a specific etiologic agent. These groups include the following:

Occupational groups	Cancer site(s)	Percent excess reported
Coal Miners	Stomach	40
Chemists	Pancreas	64
	Lymphomas	75
Foundry Workers	Lung	50–150
Textile workers	Mouth and pharynx	77
Printing Pressmen (newspaper).	Mouth and pharynx	125
Metal Miners	Lung	[illegible]
Coke by-product Workers.	Large intestine	181
	Pancreas	312
Cadmium Production Workers.	Lung	135
	Prostate	248
Rubber Industry: Processing	Stomach	90
	Leukemia	140
Tire Building	Bladder	88
	Brain	90
Tire Curing	Lung	81
Furniture workers	Nasal cavity and sinuses	300–400
Shoe Workers	Nasal cavity and sinuses	700
	Leukemia	100
Leather Workers	Bladder	150

(NCI, NIEHS and NIOSH Institutes' Report, 1978, Table 3, references omitted; Hearing Exhibit 224b).

In addition, there is an excess of certain cancers in counties where petroleum refining is carried out (Hoover, S. 7–8; Mason, *et al.* 1975, 1976). The NCI, NIEHS and NIOSH Institutes' Report pointed out that

*OSHA recognizes that over 2,400 agents have been identified by NIOSH as being "suspect carcinogens" (*Suspected Carcinogens*, HEW Publication No. (NIOSH) 78–149, December, 1978). By NIOSH's definition, this means that NIOSH has found some evidence, scientifically unevaluated by it and of varying degrees of quality and quantity, suggesting that those substances possibly have some potential carcinogenic activity, based on observations in human populations or on results from experimentation with laboratory test animals. Yet, OSHA has completed regulatory activity for only 20 of those substances since its creation on April 29, 1971. A preliminary "first-cut" scientific review of the NIOSH list by an OSHA contractor, as will be discussed below, indicates that 271 of the substances are likely to meet the proposed Category I criteria while 300 are likely to meet the proposed Category II criteria. While OSHA does not view this list as definitive, this indicates that only a relatively small fraction of the substances listed in the NIOSH and other lists of suspected carcinogens is likely to prove carcinogenic when the scientific evidence is thoroughly reviewed.

occupational exposure to radiation is also a significant cause of cancer:

"In addition to chemical carcinogens, occupational exposure to radiation is known to be a significant cause of cancer in U.S. workers. Groups at risk include radiologists, uranium miners, workers in the nuclear industry, military personnel exposed to radiation from nuclear explosions and to nuclear weapons, aircrews, and persons working at high altitudes. Persons working outdoors such as farm workers and fishermen are subject to increased risks of skin cancer associated with solar radiation. We have not attempted to make numerical estimates of expected cancer incidence in these occupations, although many millions of workers are at presumptive risk." (NCI, NIEHS and NIOSH Institutes' Report, 1978, p. 16; Hearing Exhibit 224 b)

As Dr. Arthur Upton (Director, NCI) pointed out (S. 6), the list of known carcinogenic agents includes several very large volume chemicals to which millions of workers are exposed. Similarly the list of other hazardous occupations presented above would involve several million workers. Moreover, only a small number of the industries and chemicals which might pose carcinogenic risks have ever been studied. Dr. David Rall (Director, NIEHS) pointed out that of 368 chemicals reviewed in the IARC Monograph series, only about 8 percent have been adequately studied for potential carcinogenicity in exposed humans (Rall, Director, NIEHS, S. 3–4). The same point was made in the NCI, NIEHS and NIOSH Institutes' Report (1978):

"Few industries have been investigated adequately for evaluating the possible occurrence of occupationally related cancers. Because of the insensitivity of epidemiologic surveys and various difficulties in conducting them (7), only agents and industrial processes which lead to rather large excess incidences have been identified to date. The International Agency for Research on Cancer (IARC) has an ongoing program to review data on chemicals for potential carcinogenic effects. To date, some 368 chemicals and industrial processes have been reviewed. According to a recent summary of the results of this program (8), some 26 chemicals or industrial processes have been identified as associated with increased risk of cancer in man (Table 1). This list includes a number of drugs and chemicals to which there is little or no occupational exposure in the United States. Only 8 or 9 of the 26 substances and processes listed in Table 1 involve exposure to large numbers of workers. By way of contrast, some 221 chemicals or mixtures were identified in the same survey as carcinogenic to one or more animal species. Although there is some occupational exposure to the majority of these 221 substances, epidemiological and case studies were in all cases either lacking, or inadequate to determine whether or not the substances are associated with excess cancer incidence in exposed human populations (8). Thus, adequate data are available for only a very small fraction of the substances and industrial processes which pose potential risks to exposed workers. Although it is possible that all the major hazards have already been identified, there is little reason to believe this without much more extensive epidemiologic investigations. In fact, many new processes and materials have been introduced in recent years. Some of these could be as hazardous or more hazardous than those used in the past." (NCI, NIEHS and NIOSH Institutes' Report, 1978; pp. 1–2; Hearing Exhibit 224b)

Dr. Robert Hoover (NCI) pointed out that the identification of excess carcinogenic risks in occupational groups is the rule rather than the exception:

"In summary, very few industries have received any sort of evaluation for long-term health hazards. It should be obvious then that trying to estimate the amount of cancer that is industrially related is impossible in the absence of such evaluations." (Hoover, S. 8–9)

2. Occupational Factors in the Development of Cancer in the U.S.

There was a clear consensus that cancer is a serious occupational problem and that OSHA should regulate workplace carcinogens. The percentage of all cancer that workplace cancer contributes, however, was the subject of vigorous debate in the hearings. Many industry interests, witnesses and participants cited estimates by Higginson (1969), Higginson and Muir (1976), Wynder and Gori (1977), and Doll (1977 and unpublished) that no more than 1–5 percent of total cancers in the developed countries are attributable to occupational factors.

The only attempts to document any such estimates in the Record, however, were presented in the testimony of Dr. Irving Selikoff (Mt. Sinai School of Medicine) and the NCI, NIEHS and NIOSH Institutes' Report (1978). Dr. Selikoff testified:

"Taken with other data that Dr. Nicholson has used, it suggests that this one carcinogen [asbestos] has been responsible for an extraordinary number of deaths and may be anticipated to be responsible for this in coming years, at least for the next thirty to forty years, as a result of our past inadequacies.

"Secretary Califano three or four weeks ago—maybe it ~~is five weeks ago~~ now—reported his estimates that there are now some eight to eleven million people who have been significantly exposed to asbestos and who are now at risk of asbestos disease. We have found that 20 percent of all deaths are due to lung cancer among people significantly exposed to asbestos.

"This would suggest that—let us use a round figure of around 10 million for Secretary Califano's estimate. This would suggest that somewhere around two million deaths of lung cancer are going to occur in the next thirty, forty or so years. What is that, around 50,000 a year or something like that?

"Our data—and we do not agree with the British here—indicate that somewhere between seven and nine percent will die of mesothelioma. The British say it is going to be somewhere around 11 percent. Well, it will be somewhere in between perhaps. I think our data are better. But in any case it promises to be somewhere around 900,000 deaths of mesothelioma in the next 30 or 40 years. In any one year it will be no more than, what, 10,000, 11,000 or so deaths.

"We can add the gastrointestinal, the oral-pharyngeal, the larynx, the kidney, and so forth.

"But it suggests that some 40,000 deaths a year, approximately 10 percent of all cancer deaths in this country are going to be due to this one agent, the one that happens to have been very well studied, in these next decades which face us as a result of our past inadequacies." (Selikoff, Tr. 1702–04)

Dr. Selikoff, when further asked to clarify his testimony concerning mesothelioma, stated:

"Okay. Secretary Califano, on the basis of the data available to him, estimated that there were now between 8 and 11 million Americans who had been significantly exposed to asbestos. That is a pretty big spread, and I do not know whether 8 million is right or 11 million is right. And this, by the way, does not take into account people who have been exposed in household contact circumstances, to which Dr. Nicholson alluded, nor in neighborhood circumstances, nor from the use of consumer products, you know, the guy who does his own spackling at home over the years, going to the supermarket and buying some spackle compound which contained 12 percent asbestos, et cetera.

"But let us take the between 8 and 11 million. For purposes of discussion, for round figures, let us use the term 10 million. If our data are correct that it is going to be somewhere around 8 percent, let us eliminate the British projection. That would indicate that of the 10 million that 800,000 will die of mesothelioma. But they are not going to die tomorrow nor next year. Some of them are only 25 years old now, and they are not going to die, if our other data are correct, until they are 55. About two-thirds of all asbestos insulation workers die before the age of 65. This has created quite an actuarial problem, because they have been paying into their pension funds as if they are going to live past 65 like the rest of us, but they tend not to, and the pension funds are getting too weighty.

"But be that as it may, they will be dying, I would ~~estimate, let~~ us say, in the next 40 or so years. If 800,000 are going to die in the next 40 years, it will be somewhere around, in rough figures, around 20,000 per year. It may be more [than] 30 years from now, less [than] five years from now, depending upon the duration from onset at this point.

"Q: Would you consider, Dr. Selikoff, would you consider 20,000 deaths of mesothelioma per year a major public health problem?

"A: Oh, of course." (Selikoff, Tr. 1737–38)

The NCI, NIEHS and NIOSH Institutes' Report (1978) estimated that in coming decades up to 20 percent and perhaps as much as 40 percent of cancers in the U.S. might be associated with occupational factors. These estimates were originally disputed by AIHC (Hearing Exhibit 275), although another group of AIHC consultants (Research Statistics, 1978) considered that they were somewhat inflated but within a reasonable range.

OSHA believes that resolution of the conflicting estimates is not necessary to justify action to reduce exposure to carcinogens in the workplace. This regulation was not and is not predicated on the assumption that occupational factors are responsible for any specific fraction of the cancer burden in the U.S. population. As noted above, a number of large groups of workers are already known to be at a statistically detectable excess risk for certain cancers. Even if such groups were small, OSHA would be justified, indeed required, to regulate their exposure in order to eliminate their risk of illness and death. However, it is known that these groups are not small. As Dr. David Rall (Director, NIEHS) pointed out (Rall, S.3), even if occupational factors in fact caused "only" 1–5 percent of cancer, in the U.S. this would still account for between 3,800 and 19,000 cancer deaths annually. Thus, OSHA believes that under the circumstances it may never be possible to absolutely determine the exact percentage of cancer attributable to occupational exposures. Yet OSHA rejects, for the reasons discussed, the claims that "occupational" cancer contributes less than 1–5 percent of the total cancer in the United States.

Nevertheless, because of the prominence given to this argument by several witnesses, OSHA considers it desirable to review the issue briefly. For the reasons given in the NCI, NIEHS and NIOSH Institutes' Report (pp. 5–8), OSHA places little weight on the estimates by Higginson, Wynder and Gori, and Doll.* Specifically, these estimates were based on the erroneous assumption that each cancer should be assigned to a single specific cause, were limited to the small number of known examples, and were largely unsupported by documentation or critical review of data. As the NCI, NIEHS and NIOSH Institutes' Report concluded:

"We conclude that the statement, that no more than 1% to 5% of cancers in the United States are attributable to occupational factors is based on partial use of current knowledge, reflects the one-cause one-effect fallacy—and is not particularly useful for estimating future risks. It is not even a correct reflection of the published estimates, which range up to 10% [Wynder and Gori 1977] or 15% [Cole 1977]." (NCI, NIEHS and NIOSH Institutes' Report, 1978, pp. 7–8; Hearing Exhibit 224b)

While respecting the attempts of Higginson *et al.* to estimate the "importance" of environmental or occupational cancers, OSHA agrees with the conclusion of the NCI, NIEHS and NIOSH Institutes' Report that Higginson *et al.*'s estimates of the "importance" of occupational cancer are too insecurely based and inadequately documented to serve as the basis for the assignment of any national priorities.

In contrast, the estimates of the NCI, NIEHS and NIOSH Institutes' Report were much more fully documented and included three significant methodological improvements:

(i) The Institutes recognized that most cancers have multiple causes:

"The initiation and development of cancer is a multi-phased, multi-causal process in which both external and internal factors act, probably at each of several stages, before frank, clinical cancer appears. It is likely that many, if not most, cancers are influenced by two or more different external factors acting simultaneously or sequentially. Thus, alcohol by itself appears to be a minor cause of cancer—but alcohol combined with cigarette smoking leads to risks 15 times higher than those experienced by non-smoking non-drinkers. If a drinker smoker develops cancer of the oral cavity, to which 'cause' should it be attributed? Drinking or smoking? If we could correctly identify the proportions of cancer incidence 'attributable to' each of the classes of environmental factors considered by Wynder and Gori, the sum of these percentages would be considerably higher than 100. One of the best-studied examples of interaction between exogenous agents is that between asbestos and cigarette smoke in inducing lung cancer (9). Most lung cancers 'attributable to' asbestos are probably simultaneously 'attributable to' smoking. If current theories of a multi-causal process are correct, it seems likely that a large fraction of cancers which at first appear to be 'attributable to' smoking should also be 'attributable to' asbestos, radiation, and/or other occupational factors." (NCI, NIEHS and NIOSH Institutes' Report, 1978, p. 3; Hearing Exhibit 224b)

(ii) The Institutes took into account the long latent periods for occupational cancer and recognized that the germane question is how to estimate the future consequences of present exposures:

"Another defect of the studies summarized above is that they may deal with an inappropriate question. Most appear to have been attempting to provide estimates of the fraction of *present-day* cancer incidence that is attributable to occupational exposure *in the past*, to agents that have already been demonstrated to be carcinogenic. However, such a question is of limited interest because the most important consequences of exposures in the recent past will not be manifested until some time in the future. The question that needs to be addressed is 'What is the likely contribution of *present-day* occupational exposures to future cancer incidence?' An answer to this question must be somewhat speculative, because we do not know which of the chemicals in the present-day workplace will be identified sometime in the future as causing cancer. Accordingly, to provide a basis for making appropriate estimates, we will first attempt to estimate the contribution of occupational exposure to known carcinogens in the recent past to present and future cancer incidence." (*ibid.*, p. 8)

(iii) The Institutes recognized that most occupational studies underestimate lifetime risks, because for many carcinogens excess risks remain and even increase with age after cessation of exposure:

"Most occupational carcinogens are characterized by 'latent periods' of 10 to 50 years between the onset of exposure and the clinical appearance of tumors (7). This is consistent with the multi-stage process. When occupationally related cancers are detected, they usually reflect exposures which started one or more decades in the past. Accurate numerical assessment is further complicated by the strong dependence of cancer incidence upon age and upon duration of exposure. Even in cases where an excess *risk* is detected within one or two decades, this dependence on age implies that most of the attributable cancers will not occur until later in the life span of the exposed workers, perhaps as much as 40 or 50 years after the first exposure. It is difficult to trace anyone for so long a time, and those epidemiological studies which do not follow people for a full lifetime are likely to underestimate lifetime risks. Most industrial-epidemiologic studies have not (and probably could not) follow a working population to its extinction. This problem is discussed in more detail in the Appendix, but a numerical example illustrates its importance. For many types of cancer, incidence increases approximately at the fourth or the fifth power of age (10); hence the cumulative number of cancers occurring in a population over a lifetime increases at the fifth or sixth power of age. If exposure to a carcinogen results in a constant multiplicative increase in risk at all ages, then the number of cancers occurring in an exposed group will similarly increase at the fifth or sixth power of age. Thus, for example, the number of attributable cancers occurring by age 50 would be only about one-fifth or one-sixth of that expected by age 70.

*Numerical estimates by Doll were introduced into the Record after the close of the hearing (Report of the British Royal Society Study Group on Long Term Toxic Effects, July, 1978; See AIHC Post-Hearing Brief, p.19). However, Dr. Andre McLean, an AIHC witness who was secretary of the Study Group, had earlier characterized this estimate as follows: ". . . that particular estimate was kicked around and was produced by Sir Richard Doll and Richard Peto and is a fairly informal—and I do not think that we can make much of it." (McLean, Tr. 4836).

For this reason epidemiological studies often enumerate only a small fraction of the total excess cancers attributable to an agent. Any overall assessment of the importance of occupational carcinogenesis should take this into account." (*ibid.*, pp 3–4)

Despite these methodological improvements, the NCI, NIEHS and NIOSH Institutes' Report recognized that the estimates were severely limited by inadequacies of the data base, particularly by the lack of any information on the risks associated with most industrial chemicals. For this reason, the Institutes did not attempt to make numerical estimates of future consequences of present-day exposures: the Institutes limited the calculations to future consequences of exposures in the recent past to a few well-studied chemicals, and pointed out the severe limitations even of this exercise (*ibid*, pp. 8, 16–18).

The NCI, NIEHS and NIOSH Institutes' Report divided occupational carcinogens into three groups for the purpose of estimating their potential importance:

(i) For asbestos, the report presented calculations projecting an average of 58,000 to 75,000 excess cancer deaths per year in the next 30–35 years, i.e., 13–18 percent of all cancer deaths in the United States in that period (NCI, NIEHS and NIOSH Institutes' Report, 1978, pp. 8–11).

(ii) For five other well-studied substances, the report performed rough projections based on observed site-specific risks and estimates of the number of workers exposed (NCI, NIEHS and NIOSH Institutes' Report, 1978, pp. 12–14 and Table 2). The report expressed considerable reservations about these estimates and did not in fact use them directly:

"For these reasons, the figures should not be interpreted as precise estimates of future cancers, but it is reasonable to compare them with the data derived by the same method for asbestos related cancers. At the least, the data summarized in Table 2 show that the five other agents together pose hazards similar to or greater than those posed by asbestos. The sum of the best projections (see notes to Table 2) for the five compounds is about 33,000 cancers per year, versus 13,900 for asbestos." (*ibid.*, p. 14)

(iii) For other known and potential occupational risks, the report made no estimates at all except to point out the existence of such risks (*ibid.*, pp. 15–16).

The NCI, NIEHS and NIOSH Institutes' Report concluded that it was impossible to say anything firm about the magnitude of future risks attributable to present-day occupational exposure to chemicals for which there are no epidemiological data. However, the Report added the following statement:

"There is no evidence, however, that these risks are substantially less than the risks resulting from exposures in the recent past. Although several of the most important known carcinogens have been controlled, others have not; many carcinogenic and potentially carcinogenic chemicals are still present in U.S. workplaces; the total volume of synthetic organic chemicals produced in the U.S. continues to increase rapidly. If only one of the thousands of chemicals introduced into commerce in the past 30 years proves to be as hazardous as asbestos, this could suffice to maintain comparable rates of occupationally-related cancer for decades into the future. In our view, any complacency about the future consequences of present-day exposure to uncharacterized chemicals would be unjustified." (*ibid.*, p. 18)

Because the NCI, NIEHS and NIOSH Institutes' Report overall estimates depend primarily on their estimate of the magnitude of asbestos-related cancer, it is worth reviewing the basis for this estimate:

"Asbestos as a Well-Studied Example

"The consequences of occupational exposure to asbestos in the United States have only begun to be recognized in the recent past (12–14). It has been estimated* (11) that between 8 and 11 million workers have been exposed to asbestos in the U.S. since the beginning of World War II. Of that total, approximately 1.5 to 2.5 million are presently employed. Probably a million have already died, while the remainder—between 5.5 and 7.5 million workers—were formerly employed in environments with significant asbestos exposure, including the survivors among the 4.5 million who worked in shipyards during the 1940's. Of these and other asbestos workers, approximately 4 million are believed to have had heavy exposure to asbestos (11). Epidemiological studies of workers (13–15) have indicated that, of heavily exposed workers who have already died, 20–25 percent have died of lung cancer, 7–10 percent of pleural or peritoneal mesothelioma, and 8–9 percent of gastrointestinal cancers, adding up to a total of 35–44%. These figures may be underestimates of lifetime cancer risks, because most of these workers have not been followed to the end of their life span.

"Of the 4 million heavily exposed workers, at least 1.6 million are thus expected to die of the asbestos-related cancers listed above. [In the absence of exposure to asbestos, about 0.35 million (8–9 percent) would have been expected to die of cancers at these sites.] Assuming that the excess risk to the remaining less heavily exposed workers is one-quarter of that to the heavily exposed workers (an assumption suggested by the data in ref. 16), the total number of cancers attributable to asbestos in the less-heavily exposed group would be expected to be in the range 0.4 to 0.7 million, raising the total to 2.0 to 2.3 million. Since most of these cancers will be manifested over a period of 30–35 years, the expected average number of cancer deaths associated with asbestos per year in that period will be between 58,000 to 75,000.* Such numbers would comprise 13–18% of all cancer deaths expected in the United States in the foreseeable future (assuming that total cancer deaths increase to 400,000 to 450,000 per year)." (*ibid.*, pp. 8–10)

This calculation has been contested by AIHC, basically on three grounds:

(i) that the incidence of mesothelioma ("the marker disease for asbestos") is only 10–20 percent of that predicted by the NCI, NIEHS and NIOSH Institutes' Report;

(ii) that the Institutes' Report overestimated the number of workers with heavy exposure to asbestos and underestimated the number of World War II workers who have already died; and

(iii) that both exposure to asbestos and smoking have been reduced since 1945. (AIHC *Reply*, pp. 2–3 and Appendix A; Hearing Exhibit 275 A)

OSHA does not find these objections compelling. AIHC's estimates of mesothelioma incidence were based on the NCI's "SEER" program, whose sample does not include several of the cities or states where asbestos use has been greatest. The data on the number of workers exposed heavily and surviving to date are certainly imprecise, but it is unlikely that they are too high even by a factor of two. OSHA notes that an AIHC sponsored review considered that the asbestos estimates might be too high by up to a factor of two (Stallones and Downs, 1978). OSHA notes also that the leading specialist in asbestos-induced cancers, Dr. Irving Selikoff (Mount Sinai School of Medicine) himself estimated as many as 50,000 excess deaths per year among highly exposed workers, a figure very close to that in the NCI, NIEHS and NIOSH Institutes' Report. Accordingly OSHA regards the Institutes' estimates of asbestos-related cancers as reasonable, and unlikely to be too high by more than a factor of two. Because of the conservative way in which the NCI, NIEHS and NIOSH Institutes' Report extrapolated from the asbestos estimates,* OSHA believes that their final estimate (that up to 20–40 percent of U.S. cancers in coming decades will be occupationally related) is reasonable.** Finally, it should be noted that even if the number of workers exposed to asbestos was overstated, the

*AIHC's detailed critique of the calculations in the Institutes' Report for other carcinogens is misplaced, because the results of these calculations were not in fact used directly to derive the overall estimates.

**The results of the Stallones *et al.* study are consistent with the NCI, NIEHS and NIOSH Institutes' Report.

NCI, NIEHS and NIOSH Institutes' Report dealt only with six substances instead of the 18 substances identified by Tomatis *et al.* (1978) as confirmed human occupational carcinogens, thus perhaps understating the risks found in the American workplace. Likewise, the occupational categories for which no single agent was identified were not factored into the calculations.

The NCI, NIEHS and NIOSH Institutes' Report pointed out that its conclusion that a substantial fraction of cancers in the United States is occupationally related is not inconsistent with conclusions that substantial fractions of cancers are also associated with other factors, such as cigarette smoking and diet.*

"These estimates do not diminish the importance of other contributing factors to cancer risk such as smoking, diet, and perhaps urban-rural differences. While much of the data on occupational cancer risk considered in this paper do not specifically consider factors such as smoking (except for asbestos) and diet, it is also fair to state that the prevailing body of data linking smoking and diet with cancer risk does not adequately consider the contribution of exposure to occupational carcinogens. This is largely because the available scientific methodologies do not facilitate adequate consideration of all contributing factors in any single study or approach. Until recently most scientists did not take into account the multiple etiologies and the multi-stage nature of cancer. In retrospect, it is likely that cancer risk is a function of multiple interacting factors. Past assessments, unfortunately, generally failed to consider adequately one of the most important, and preventable, risk factors, exposure to carcinogenic agents in the workplace." (NCI, NIEHS and NIOSH Institutes' Report, 1978, p. 22; Hearing Exhibit 224b).

3. Opportunities for Prevention of Occupational Cancer

The importance of the recognition that occupational factors are associated with a significant fraction of cancer incidence in the United States is that most occupationally related cancers can be prevented by reducing exposure. As the NCI, NIEHS and NIOSH Institute Report expressed the matter:

"The estimates of cancer attributable to occupational exposure given here should be viewed as pointing up the opportunities that exist to prevent disease in future generations. The causes of cancer are multiple, with more than one factor contributing to cancer risk. In such a situation, any percentage accounting of contributing causes to cancer well exceeds 100%. To prevent cancer, one must concentrate on causative factors that can be reduced so that we can decrease the burden of disease in future generations. It has been argued that present day asbestos workers are at lower risk than earlier workers. Opportunities to reduce risks and subsequent disease in other occupations are at hand." (Institutes' Report, 1978, p. 23)

The opportunities for prevention of cancer were also emphasized by several other witnesses, including Dr. Rall (Director, NIEHS) (S. 6), Dr. Upton (Director, NCI) (S. 2–8), Dr. Epstein (Univ. of Illinois) (S. 11–26), Dr. Holmberg (Swedish NBOSH) (S. 7–8), and Dr. Shubik (Eppley Institute, Univ. of Nebraska) (S. 1).

Recognizing that most cancers have multiple causes, it is theoretically possible to prevent them in more than one way. For example most asbestos related lung cancers occur in workers who also smoke (Selikoff, Tr. 1702). According to Dr. Selikoff's data, it would be possible to prevent about as many lung cancers by eliminating smoking as by eliminating exposure to asbestos; eliminating both would yield additional benefits.

During the proceeding some parties appeared to suggest that OSHA should regulate cigarette smoking in the workplace rather than control workplace exposures to carcinogens. OSHA agrees that cigarette smoking is a grave public health problem. However, there is no evidence that by controlling cigarette smoking in the workplace, cancer from occupational exposures will cease. Therefore, OSHA is required to regulate occupational carcinogens regardless of whether it regulates the smoking of cigarettes in the workplace.

The question of regulating cigarette smoking is a complex social and policy issue that goes far beyond the purview of OSHA. It is a personal habit which is likely to continue outside of the workplace even if controlled in the workplace. Other regulatory agencies have the authority to regulate the general sale and use of cigarettes. On the other hand, OSHA can and does control smoking in the workplace to prevent employees from smoking in the presence of occupational carcinogens. OSHA may well determine, on the basis of scientific review, that "passive" exposure to cigarette smoke in the workplace constitutes a potential occupational carcinogenic risk which should be regulated under the terms of the policy. It may be that in establishing its priorities OSHA will give higher priority to substances and physical agents that are occupationally released than to cigarette smoking which is a general exposure that happens to take place in workplaces. In any event, since OSHA is not establishing a priority list as a part of this document, the question of the priority of cigarette smoking in the workplace will be decided when OSHA in fact determines its priorities.

H. TRENDS IN CANCER INCIDENCE AND MORTALITY

Some parties to this proceeding claimed that because the proposal stated that: "As the rates increase, the causes elude us", OSHA was predicting that an epidemic of cancer was about to occur. This is inaccurate. OSHA did not imply nor intended to imply any such epidemic. Nor did OSHA "impl[y] that the use of industrial chemicals is the new and substantive causative factor in this epidemic" (Post Hearing Brief of the American Iron and Steel Institute, p. 28). In any event, OSHA does not believe that this issue is revelant to whether OSHA should establish a cancer policy. Cancer is a serious problem, and, as Dr. Schneiderman (NCI) has pointed out, this Nation has made commitments in the past to eradicate specific diseases, although the incidence or mortality rates from such diseases had gone down. Thus, OSHA does not believe that it is required to show that cancer incidence in this country is on the rise before promulgating a policy such as encompassed by this document today. Indeed, with the rapid increase of the use of synthetic organic substances, as pointed by Dr. David Rall (Director, NIEHS), such a policy as this one adopted today will be needed to provide a prudent degree of worker protection.

As other causes of death have been reduced in importance in this century, deaths from cancer have increased steadily. In 1900, pneumonia and influenza headed the list of the ten leading causes of death in the U.S., followed by tuberculosis, infectious gastrointestinal diseases and heart disease. Cancer was only number eight, accounting for less than 4% of all deaths. By 1940, cancer had climbed to the second leading cause of death after heart disease, accounting for about 18% of all deaths, and it has remained in second place ever since. By 1975, cancer caused 20 percent of all deaths in the United States, and it is now estimated that about 27 percent of the present population will die of cancer. The total number of deaths from cancer has been increasing at more than 2 percent per year and reached 385,000 in 1977 (USDHEW, 1974, Levin, *et al.*, 1974; Monthly Vital Statistics Report 1978; Epstein, S. 3–8; Schneiderman *et al.*, 1978).

Although much of the increase in cancer mortality has resulted from the increasing average age of the

*AIHC's criticism of this conclusion as "double or triple accounting" (AIHC *Reply*, p. 12) is not consistent with the scientific consensus on the multi-causal nature of carcinogenesis, as discussed above, and demonstrates a serious lack of understanding of the issue.

population, this is not the only factor at work. Age-specific death rates for a number of types of cancer have increased significantly since 1951 (Jones, S. 23–45). The age-adjusted * death rate for malignant neoplasms increased from 79.6 per 100,000 in 1900 to 128.4 in 1966, 130.7 in 1971, and 132.3 in 1976 (Schneiderman, 1978, Table 1). Although the age-adjusted *mortality* rate from cancer has thus been increasing by only about 0.3 percent per year, the age-adjusted *incidence* rate has been increasing by about 1.6 percent per year (*ibid.*, Table 3). The difference reflects three factors: (i) the inclusion in the incidence figures of cancers that are not immediately fatal or not fatal at all; (ii) improvements in early diagnosis and treatment for certain cancers which prolong the interval between diagnosis and death; (iii) misdiagnosis of some cancer deaths as due to other causes.

A very large volume of testimony was presented at the hearing on trends in cancer incidence and mortality, and their hypothetical relevance to the problem of occupational carcinogenesis. Detailed presentations were made in the statements of Dr. Marvin Schneiderman (NCI), Dr. Samuel Epstein (Univ. of Illinois), Mr. Richard Peto (Univ. of Oxford), Dr. Bo Holmberg (Swedish NBOSH), Dr. Johannes Clemmesen (Danish Cancer Registry), Dr. Hardin Jones (Univ. of San Francisco), and in the presentations of AIHC and other industry groups. Most of this testimony was devoted to arguing two major points: (i) whether there is or is not a cancer "epidemic", and (ii) whether the current increase in cancer mortality is largely or wholly attributable to smoking. For example, AIHC summarized its position as follows:

"The reasons advanced by OSHA to support its proposal imply that this nation is suffering an epidemic of cancer and that the epidemic is largely if not entirely attributable to increased manufacture and use of industrial chemicals. Factual evidence does not support that view. If we use the turn of the century as a time against which to compare today's cancer problem, there has indeed been an increased in the incidence of cancer—but the increase is predominantly attributable to (1) greater longevity (the incidence of cancer increases with age), and (2) pandemic cigarette smoking. With adjustments for these two forces, as documented by both the American Cancer Society and United States government statistics, no overall increase in cancer incidence appears for the United States." (AIHC Alternative, p. 1) (Footnotes omitted)

OSHA regards this testimony as both in error and irrelevant to the issues in this proceeding, for the following reasons:

1. The need for this regulation was not and is not predicated upon the existence of a cancer "epidemic", nor even upon the existence of trends in cancer mortality. Even if the trends in cancer incidence were uniformly downward, the existence of demonstrable carcinogenic risks in U.S. workplaces would require regulatory action by OSHA, under the terms of the Occupational Safety and Health Act.

2. Gross statistics on cancer mortality are an extremely insensitive tool with which to explore the relationship between occupational exposure and cancer risk. Most of the industry testimony on trends in cancer mortality was based on the results of surveys in 1947, 1961, and 1969–1971. In view of the 20–30 year latent periods for occupational cancers, it is extremely unlikely that these statistics would reflect the consequences of exposures later than the 1940's.* As the NCI, NIEHS and NIOSH Institutes' Report (1978) pointed out, the major public health disaster of asbestos-related cancer may be only just beginning to be reflected in overall cancer statistics, despite 37 years of heavy exposure (Institutes' Report, 1978, pp. 10–11, 20).

3. Summary statistics on cancer mortality obscure many important trends that would need to be considered in testing hypotheses about the importance of occupational factors. For example, trends in mortality may be opposite to trends in incidence; trends are frequently different in males and females, in blacks and whites, and in older and younger persons (Schneiderman, NCI, Post-hearing Comments; Jones, Univ. of San Francisco, S. 23–45).

4. With the recognition that most cancers are caused by multiple factors, it is scientifically incorrect to argue that specific trends in cancer mortality are attributable exclusively to cigarette smoking and that the influence of other factors can therefore be excluded.†

Among the statements on cancer statistics presented during the proceeding, most were based on the results of the Second and Third National Cancer Surveys, conducted in 1947 and 1969–71 respectively (Dorn and Cutler, 1959; NCI, 1975). Only the testimony of Dr. Marvin Schneiderman (NCI) discussed in detail data generated through 1975 by the NCI's SEER program. As Dr. Schneiderman pointed out (Post-hearing Comments, p. 2 and Appendix B), the SEER data are better than the earlier data in three respects:

(i) they are based on better diagnostic data, especially for older persons; (ii) they reflect cancer incidence rather than mortality; (iii) they provide information on trends since 1970:

"1. The National Cancer Institute's SEER program provides a sample of cancer incidence in the United States, providing data that are internally consistent and comparable to the data provided by the Third National Cancer Survey (Appendices B and C). I believe that these are the only data in the hearing record that provide measures of recent trends in incidence of cancer (1970–1975).

"2. The SEER data on cancer incidence are developed from a review of hospital (and other) records and are likely to give more accurate diagnostic information than mortality data, which are derived from death certificates (Appendix B, p. 3). In particular, the SEER data are likely to be reliable indices of trends in cancer incidence in persons over 65, unlike the mortality data for the United Kingdom on which Richard Peto has commented." (Schneiderman, Post-hearing Comments, p. 2)

According to the SEER data, (Schneiderman, Post-hearing Comments, Appendix B, Table 2), total age-adjusted cancer incidence in white males increased by about 8 percent between 1970 and 1975. Restricting attention to cancers at sites thought likely to affected by industrial carcinogens, the increase in incidence in white males was 11% in the 5-year period. The largest increases were in melanoma (37%), lymphoma (17%), bladder cancer (17%) and lung cancer (7%). At least in the bladder and lung, increases in incidence in black males have been much greater than those in white males (Epstein, S. 7, citing Cutler and Devesa 1973).

Since the sites showing the largest increases in cancer incidence in the period 1970–75 are sites at which occupationally-related cancers tend to be observed (NCI, NIEHS and NIOSH Institutes' Report, Tables 1 and 3), these data are consistent with a hypothesis that exposure to industrial carcinogens increased in importance in the 1940's or 1950's. AIHC (Post-hearing Brief, pp. 18–19) and its witnesses argued instead that most of the increases were attributable to cigarette smoking and therefore

* An "age-adjusted" death rate is the number of deaths per 100,000 persons expected in a population with a standardized age distribution. Comparison of age-adjusted death rates eliminates effects due to changing age distribution in the population, but it does not eliminate effects due to changes in the age distribution of cancer deaths such as those tabulated by Jones (S. 23–45).

* The arguments of Dr. Jandl (Harvard Univ.) (S. 2–10) were incorrect for this reason, among others.

† The increase in asbestos-related lung cancer is usually dismissed as due to smoking, while effects of asbestos on the incidence of stomach and colon cancer are masked by long-term downward trends (*id.*). Reported deaths from mesothelioma have not yet shown an increase in the U.S. statistics (AIHC *Reply*), although they have increased in the United Kingdom (Doll, Annex E(b) to Peto Statement).

should be subtracted out of the cancer statistics. However, such a position is not convincing to OSHA.* As the NCI, NIEHS and NIOSH Institutes' Report (1978) pointed out:

"To subtract all the 'smoking-related' cancers from the total is sophistry, because at least two of the sites in question are precisely those in which 'occupationally-related' cancers are best recognized. Many of the smoking-related cancers should be simultaneously attributable to occupational factors. On a per capita basis smoking among adults is declining and this should result in a decline in the smoking-related cancers—but none of this is factored in when all 'smoking-related' cancers are removed from the total." (NCI, NIEHS and NIOSH Institutes' Report, 1978, p. 20; Hearing Exhibit 224b)

Although subtracting out smoking-related cancers is likely to subtract out many occupationally-related cancers also, Dr. Schneiderman nevertheless applied AIHC's proposed procedure to the SEER data on cancer incidence. Using artificially high figures for the fraction of cancers "attributable" to smoking and sunlight, Dr. Schneiderman found that the incidence of cancers not attributable to these factors had increased by 7 percent since 1970. The incidence of cancers thought likely to be industrially related had increased by 12 percent (Schneiderman, Post-hearing Comments, Appendix B). He concluded:

"3. Cancers that are possibly industrially related increased in incidence in white males between the 1947 and 1970 National Cancer Surveys. The annual rate of increase after making generous allowance for the effects of cigarette smoking ranged between 0.4% and 1.0% per year (Appendix B, p. 6 and Table 1).

"4. In the time period 1970 to 1975 this increase ranged between 1.4% and 2.3% per year (Appendix B, p. 6 and Table 2).

"5. Conclusions (3) and (4) were unchanged when approximate allowance was made for changes in smoking habits and in tar content (Appendix B, p. 6). In fact, the recent reductions in the tar content of cigarettes probably mean that I overestimated the contribution of cigarette smoking to the recent increase in cancer incidence." (Schneiderman, Post-hearing Comments, pp. 2–3)

OSHA concludes that AIHC's argument was factually incorrect: even after over-compensating for the effects of cigarette smoking, the *incidence* of occupationally-related cancers has increased since 1947 and the increase has accelerated since 1970. As pointed out above, however, these facts are not *directly* relevant to this regulation, because cancer causing substances must be regulated in the workplace, regardless of whether general rates of some types of cancer are increasing. Nevertheless, if rates are indeed going up, and occupational sources are responsible for a significant portion of the cancer rates, it would reemphasize the urgency of taking measures now to reduce exposures to carcinogenic agents in the workplace.

*Dr. David Rall (Director, NIEHS) described the assignment of a class of cancers to a single causative factor as "unscientific and reductionist" (S. 4).

PART B.

IV. EVIDENCE DERIVED FROM THE HUMAN EXPERIENCE

As pointed out in the proposal, the scientific and policy determination that a substance, or combination of substances; poses a qualitative carcinogenic hazard to humans can be based upon three types of evidence:

1. Evidence derived from the human experience;

2. Evidence derived from experimental long term bioassay results in mammalian laboratory animals (usually rodents); and/or

3. Supportive evidence, derived from studies of chemical structure and short-term or other tests, that correlate with carcinogenicity.

A. OSHA'S PROPOSAL

In the proposed regulation, OSHA defined a "potential occupational carcinogen", among other things, as:

". . . any toxic substance which (1) [c]auses, at any level of exposure or dose, as the result of any oral, respiratory, or dermal exposure, or any other exposure which results in the systemic distribution of the substance under consideration in the organism tested, an increased incidence of benign or malignant neoplasms, or a combination thereof, in (i) humans or (ii) in one or more experimental mammalian species, or (2) in a statistically significant manner decreases the latency period between exposure and onset of neoplasm in (i) humans or (ii) in one or more experimental mammalian species." (42 FR 54184)

Insofar as human studies were concerned, this proposed definition had two important features. First, the preamble explained that OSHA proposed to utilize positive evidence for carcinogenicity in either humans or in experimental animals as at least the basis for a presumption or inference of a qualitative hazard to humans. Second, by using the word "causes," OSHA anticipated the use of reasonable, scientifically evaluated evidence to determine a causal association between exposure and effect. Much of this section of this preamble is concerned with the nature of epidemiologic evidence and the establishment of causation by the use of human studies. Perhaps the best discussion of the role of scientific judgment in establishing causation was that of Dr. Umberto Saffiotti (NCI):

1. *"Causes"*. The definition begins by stating that "Potential Occupational Carcinogen" means any toxic substance which *causes* . . . (neoplasms).

"Let us try to understand what is involved in the concept of causation in the recognition of carcinogenic effects. In life sciences, 'causation' implies an inference of sufficient condition to bring about a temporal sequential relationship between two events. In the case of carcinogens, the two events are the exposure of an organism to a given agent and the induction in that organism of a neoplasm. Studies on the concept of causation in biology emphasize its aspect of inference from a limited number of observations and therefore its inherent element of probability (Russel, 1948). Determining that an agent is capable of causing a given neoplastic response is the outcome of a complex judgmental activity, involving evaluation of many different factors, such as knowledge of the chemical and biological systems under consideration, determination of adequacy of the conditions of observation, qualitative and quantitative evaluation of the morphology and function of the observed organisms and of their target tissues."

"A judgment of causality in carcinogenesis may be based not only on the recognition of an excessive number of neoplasms in the exposed subjects but also on other factors, such as the observation of a pattern of pre-neoplastic and neoplastic lesions in a logical temporal sequence, information about the transport of the etiologic agent to the target cells, and knowledge about its chemical reactivity. The judgment will derive from a multiplicity of direct and indirect observations which combine with general knowledge of the phenomena under study in the mind of the expert who is making this judgment. In this respect this process is similar to that of a physician diagnosing a disease from a multiplicity of observations and their logical analysis. A chemical agent should not be judged carcinogenic solely on the basis of a cursory 'tumor count', without thorough evaluation of the conditions of exposure and of host response. A simple tumor count however, if markedly abnormal, can raise a considerable level of suspicion. Concurrence and reproducibility of the observations are important elements for this assessment. The judgment of causality also includes a consideration of possible interfering factors which may produce false appearances of a cause-effect relationship, such as the presence of highly carcinogenic impurities in test substances, or—on the other side—the presence of intercurrent diseases in the test animals which may prevent the manifestation of neoplastic response.

"The judgment of carcinogenicity needs to be made by competent, experienced and objective professionals after analysis of all the relevant evidence. It goes without saying that this judgment should be objective and immune from conflicts of interest.

"I believe that the judgmental aspect of the process of carcinogen identification is

embodied in the proposed OSHA policy by its very use of the term 'causes', by its inclusion of provisions for a discretionary evaluation [e.g., [Section] 1990–110(b):' 'if * * * the Secretary finds * * * any other evidence * * * sufficient to convince him * * *') and particularly by its provisions for rebuttal of the classifications." (Saffiotti, S. pp. 6–8)

In the discussion of human studies in the preamble to the proposed regulation (42 FR 54155–54156), OSHA placed primary emphasis on the practical limitations of human studies and on the difficulties involved in scientifically establishing causation or even an association, as pointed out below.

Firstly, it was argued that carcinogenicity testing by prospective studies would not be suitable because of moral constraints against human experimentation, as well as the problems of long-term follow-up (due to the long latency period of cancer development, often several decades) and of controlling for exposure to other toxic materials (or other types of "confounding variables").

Secondly, it was argued that retrospective studies, while more readily available at the present time for evaluation, tend to have more problems in evaluation and interpretation, with "negative" studies the most difficult to interpret. Because of the time lapse between exposure and effect, retrospective studies cannot prevent exposure of some workers to carcinogenic substances, except as a basis for further action. Reliability of data generated by these types of studies was stated to be often difficult to assess for the following reasons: (1) due to individual variability in susceptibility to carcinogenic agents, effects are difficult to assess unless large study populations are used; (2) the long latency period makes detection of cause-effect relationships difficult; detection is further hindered by the difficulties in follow-up of a mobile worker population; and (3) it is difficult to link an effect with exposure to a single compound due to the occurrence of multiple exposures, difficulties in defining levels of exposure, and the possibility of additive, synergistic or inhibitory effects of these multiple exposures.

For these and other reasons, OSHA proposed to place little weight on purportedly negative results obtained in epidemiologic studies. Indeed, OSHA specifically stated that positive results from animal tests, would, in general, outweigh "negative" results from epidemiologic studies:

"And, it should be noted that certain chemicals may be carcinogenic in certain species, including man, but not in others. For example, betanaphthylamine, a known carcinogen in man, monkeys and dogs, is not apparently carcinogenic in rats or rabbits. Hence, positive studies in any mammalian species will, as a general rule, always supersede negative findings in another species." (UICC 1969, p. 18; NCI, 1970, p. 2; NCAB report, p. 9)

"Thus OSHA believes that, as a practical rather than a theoretical matter, positive animal data should supersede negative human data, in general, because of the inherent defects in such human studies, as pointed out above." (42 FR 54161)

At the outset, two points should be noted. First, in the preamble to the proposal, OSHA devoted comparatively little attention to discussion of positive results obtained in epidemiologic studies. OSHA assumed that little discussion of positive studies was needed, because where a positive study existed, its relevance to human risk would be clear. This lack of emphasis on positive studies, combined with extensive discussion of the limitations of "negative" studies, was mistaken by some participants as an intention not to use results of epidemiological studies, whether positive or negative. The discussion below attempts to enunciate OSHA's position more clearly in that regard. Second, because of the problems inherent in proving a "negative", as discussed below, some confusion arose. OSHA therefore uses the term "non-positive" to set forth more clearly the intent of this set of regulations promulgated today.

B. THE PUBLIC'S RESPONSE

A large number of witnesses and participants addressed the use of human studies in identifying and classifying carcinogens. OSHA notes initially that no witness or participant objected to the use of clearly positive results in human studies as an indicator of risks to other exposed persons. Apart from comments which discussed the "importance" of occupational exposures to chemicals as causes of cancer in the United States (see above), or presented the results of epidemiologic studies in specific industries, four broad types of issues were raised in the Record:

1. Many witnesses objected to what they interpreted as the downplaying of the importance of human studies in the proposed regulation.

2. There was considerable confusion in the Record about the types of information which human studies can provide and their inherent limitations.

3. Some witnesses pointed out difficulties in establishing positive results in epidemiologic studies, and some urged OSHA to adopt specific criteria for the evaluation of positive studies.

4. Many witnesses claimed that there are valid non-positive epidemiologic studies and that these should outweigh positive evidence of carcinogenicity of the same chemicals obtained in animals.

In response to these comments, OSHA has reviewed the Record in detail and will discuss these issues in greater depth below. In this discussion, OSHA places primary weight on the testimony of witnesses who are professional epidemiologists and statisticians, including Dr. Marvin Schneiderman (NCI), Dr. Robert Hoover (NCI), Dr. John Berg (Colorado Regional Cancer Center), Mr. Richard Peto (Oxford Univ.), Dr. Johannes Clemmesen (Danish Cancer Registry), Dr. Robert Morgan (Univ. of Toronto), Dr. Irving Kessler (Johns Hopkins Univ.), Dr. David Schottenfeld (Cornell Univ), Dr. Sidney Pell (DuPont), Dr. David Wegman (Harvard Univ.), Dr. Irving Selikoff and Dr. William Nicholson (Mount Sinai School of Medicine), Dr. Bo Holmberg (Swedish National Board on Occupational Safety and Health), Dr. P. J. Lawther and Mr. Robert Waller (St. Bartholomew's Hospital Medical College).

1. General Arguments for the Use of Epidemiologic Data

At the outset, it should be noted that not one party to this proceeding suggested that OSHA should ignore scientifically evaluated positive human data. To the contrary, several parties argued that OSHA should place much more weight on human studies, at least for limited purposes. For example, AIHC argued as follows in its Alternatives Proposal:

"OSHA is correct in recognizing that most epidemiologic studies which claim to demonstrate—even qualitatively—that an excessive incidence of cancer is caused by a single chemical are suspect because of: (a) mixed chemical exposures; (b) unknown, nonoccupational exposures (*e.g.*, smoking); and (c) poor estimations of exposure levels. However, studies which *do not* show excessive cancer incidence ('negative studies') are seldom criticized from these standpoints. Therefore, any well-executed study utilizing universally accepted techniques deserves consideration in the categorization of chemicals. In fact, it should be the primary decision-making criterion."

"The AIHC proposal would attribute more significance to available epidemiologic data (human experience) than would the OSHA proposal which would even subordinate any such negative data to positive results seen in an experimental bioassay. Since human data are free from the difficulties of extrapolating from animals, it is quite arbitrary and otherwise unscientific not to use these data whenever they are available."

"Human data could play a significant role in several ways. First, such data could suffice to classify a substance as a known human

carcinogen; it is recognized that relatively few chemicals would be so classified. Second, where appropriate, such data, with exposure level information, could indicate potency. On the other hand, such data could in some cases preclude carcinogenic classifications that might otherwise seem indicated on the basis of positive animal data. More generally, such data must be considered relevant, along with the results of animal studies, in any risk assessment."

"There is good reason to attribute significance to epidemiologic data, whenever such data are available. For example, aflatoxin is one of the most potent carcinogens in various mammalian species, but there is ample epidemiologic evidence that, where the material is not ingested in gross quantities it does not produce harmful effects in man, despite widespread exposure to it in peanuts, corn, maize and sorghum."

* * * * *

"Negative human data on the toxicity of carcinogenic materials are seldom seen in scientific journals, and certainly never in the popular press. These data are seldom compiled as there has been little incentive for making them known—much less for developing more data—since, as the OSHA proposal demonstrates, little importance is attached to this information relative to positive animal studies. The AIHC proposal would encourage the compilation and disclosure of such data, and would in many cases provide a better factual and scientific basis for rulemaking than can be provided by extrapolation from animal data." (AIHC Alternative, pp. 39–42)

Reserve Mining Company argued as follows:

"A discipline such as epidemiology, which has 'provided the firmest scientific base on which practical political decisions can be made' relative to the prevention and treatment of cancer, should not be disgarded (*sic)* as without evidentiary value. The procedural process by which OSHA is attempting, through these proposed regulations, to establish irrebuttable presumptions, and the legal infirmities of such an attempt, are described in subsequent sections." (Reserve Mining, S. 15)

The American Iron and Steel Institute stated:

"A second scientific concept underlying the Generic Cancer Policy is the notion that positive results in animal studies should always supersede negative human epidemiological data. This decision to ignore negative epidemiological data drew strong criticism from a variety of witnesses. It was pointed out that epidemiological studies are the most relevant and probative evidence of human biological responses and that they are 'naturally more appropriate for assessing human risk' than are laboratory animal tests.

"Thus, it makes no sense to ignore epidemiological data where it is available. Indeed, by refusing to recognize the significance of such data, OSHA will discourage interested persons from sponsoring epidemiological studies." (AISI, Post-hearing Brief, pp. 71–72; Hearing Exhibit 250) (Footnotes omitted.)

Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska) made the following critical comment:

"The approach taken in the OSHA document is entirely negative and would seem designed to discourage the in-depth collection of additional epidemiologic data. It would appear to be retrogressive not to attempt to acquire as much data as possible and to recognize the potential uses that may arise." (Shubik, S. 13)

Dr. Johannes Clemmesen (Danish Cancer Registry) commented as follows:

"The OSHA proposal confines epidemiology to a very minor role in its scheme of regulation. Indeed OSHA proposes to ignore negative epidemiology where there is positive animal data. I believe this to be an unsound approach. While epidemiology has its limitations, human data where available should be used as a regulatory tool. Since the ultimate question for OSHA as well as for public health in general, is the effect of a substance on humans, it is difficult to conceive how one could even consider ignoring relevant human experience. Given the difficulties and limitations of animal tests and extrapolation therefrom to humans, epidemiology becomes a critical body of information which needs in all cases to be carefully evaluated." (Clemmesen, S. 11)

Dr. Douglass Lloyd (Connecticut Dept. of Health) argued as follows:

"OSHA is relying on many authoritative publications and conclusions of scientific committees in order to provide scientific support for its categorization of toxic substances. It would therefore seem appropriate to accept the results of pertinent epidemiologic studies if properly executed, irrespective of whether the results are positive or negative." (Lloyd, Tr. 8322)

Dr. Fred Hoerger (Dow Chemical) commented:

"Since human epidemiologic data are free from the uncertainties of extrapolation from animal tests, it seems quite unreasonable not to use valid data when they are available. Such data reflect what happens in the real world and may supply results different from what might be suggested by animal tests alone." (Hoerger, Tr. 3616)

As pointed out above, much of this criticism conflicts with the proposal itself. OSHA did not in fact propose to "confine epidemiology to a very minor role," nor to "ignore epidemiological data where it (*sic*) is available"; nor would epidemiology be "disgarded (*sic*) as without evidentiary value". To the contrary, as pointed out, OSHA proposed to place great weight on positive studies, even where they are not fully conclusive:

"The basis for these criteria initiating a Category I classification are predicated upon the discussions above and here. First, despite the inherent limitations of epidemiological studies in humans, where such studies indicate positive results, even where there is a small cohort of workers, OSHA believes that exposure to such a substance gives rise to great concern. Thus, the proposed set of regulations provides that such evidence in humans at least presumptively initiates a Category I classification, unless the evidence is "only suggestive" in which case the evidence initiates the Category II classification. It is only where the human evidence is "totally inadequate" that OSHA will classify the toxic substance as a Category III toxic substance. OSHA believes that responsible public regulation in matters concerning human health requires no less action or caution." (42 FR 54170)

In fact, OSHA intends to place weight on human studies wherever they provide germane and probative scientific information about potential hazards (or the lack thereof), and that includes "non-positive" results as discussed and qualified below. Many of the comments quoted above appear to reflect a lack of appreciation of the limitations of epidemiological studies, which will be discussed in more detail below.

It had been OSHA's intention at the time of the proposal to regulate chemicals as potential carcinogens based on scientifically evaluated positive epidemiologic studies. This is made clear in the proposed regulation itself. Sect. 1990.110 stated that: "A presumption exists that a toxic substance shall be classified by the Secretary as a Category I Toxic Substance if: (a) the toxic substance meets the definition of a potential occupational carcinogen in (1) humans . . ." Sect. 1990.120 stated that "a toxic substance shall be classified by the Secretary as a Category II Toxic Substance" if the toxic substance meets the definition of a potential occupational carcinogen" in studies in test animals or humans . . ."

As pointed out above, OSHA assumed that reliance upon scientifically evaluated positive epidemiologic evidence would not be controversial and therefore placed primary emphasis in the proposal on the problems presented in carrying out epidemiologic studies and the special difficulties presented by "non-positive" epidemiology. Some participants, as the above discussion indicates, misinterpreted OSHA in regard to the use of positive epidemiology and believed that OSHA intended to disregard it.

As discussed above, epidemiology can be a powerful tool in indicating the carcinogenicity of a substance, or a combination of substances. All parties addressing the issue recognized this, as the discussion above reflects. They recommended that OSHA make use of suitable positive epidemiologic data for regulatory purposes when such evidence exists. This final set of regulations

carries out OSHA's intention and the recommendation of those participants, by regulating substances as Category I or II potential carcinogens based on suitable positive epidemiological data, where available.

The discussion in sections 2 and 3 below deals with the nature of the epidemiologic method and its strength and importance in identifying carcinogens for regulatory purposes. Section 4 points out some of the limitations of the epidemiologic method and how they can be overcome, at least when strong positive associations exist. The discussion in Section 5 demonstrates that it is not possible to set rigid criteria for judging positive epidemiologic studies, but rather that this requires good professional judgment. Section 5 also points out that positive epidemiologic studies can be valid indicators of the carcinogenicity of substances even though they do not meet all the criteria of an ideal epidemiologic study. This is because the demonstration of a large enough excess risk will more than outweigh the likely effects of confounding factors which might exist in the study.

After the discussion of the issues concerning positive epidemiology, there is an extensive discussion of the issues concerning epidemiologic studies which result in "non-positive" determinations. This discussion will set forth the scientific reasons why OSHA believes that, as a general matter, only little weight, if any, can be placed on such studies.

2. Nature of the Epidemiologic Method

In the preamble to the proposed regulation, epidemiologic studies were defined as:

> "* * * comparing cancer risk for selected groups of individuals exposed to known agents with the risk for a similar population that either has not been exposed to the same agents or has been exposed but at a significantly lower level." (42 FR 54155)

Epidemiology has been defined in standard textbooks introduced into the Record as ". . . the study of the distribution and determinants of disease prevalence in man" (McMahon, 1970, p. 1, Reference 1 to Hoover Statement), or as ". . . the study of disease in relation to the characteristics of the groups of persons in whom it occurs." (Lilienfeld *et al.*, 1967, p. 3; Reference 16 to Bates Statement). It focuses not upon any single individual but upon groups of individuals.

Basically, evidence of carcinogenicity in humans can be derived from two types of epidemiological studies, namely: (1) descriptive epidemiologic studies in which the morbidity or mortality due to cancer in human populations is found to vary (spatially or temporally) with exposures to the agent and (2) analytical epidemiologic studies (e.g., case-control or cohort studies) in which individuals' exposures to the agent are found to be associated with an increased risk of cancer. A "cohort" study is one in which the frequency of various types of cancer in a group of workers exposed to a substance is compared to that in a "control" group not so exposed. The exposed and control groups are matched, to the extent possible, in terms of age, sex and other characteristics such as smoking history. The control group may consist of another group of workers with different exposure history or of a sub-category of the general population with the same age and sex distribution as the exposed group. A "case-control" study is one in which a group of patients with a certain type of cancer is compared to a group of controls without cancer but otherwise similar to the patients in age, sex, smoking history and other characteristics. By interviewing patients and controls, it is possible to seek consistent differences between the groups in their exposure to factors operating in the past which might have contributed to the induction of cancer. In the occupational context, associations are sought between occurrence of cancer and prior employment in certain types of jobs. Epidemiologic studies, when done properly, are the most direct—and, if positive, obviously tragic—measure of the carcinogenicity of an agent since humans themselves were the subjects of these studies.

In contrast to the controlled experimental study of animal species, epidemiologic studies of necessity rely upon the untoward effects of unplanned exposures in the past. For that reason, it may be difficult, in any one epidemiologic study, to account for all potentially confounding variables. Thus, while a single epidemiologic study may strongly suggest a cause-effect relationship, the most scientifically convincing evidence of causality from epidemiologic studies generally is derived from more than one independent study done under diverse circumstances which result in positive findings.

Any epidemiologic study showing or not showing a positive association between exposure to an agent and an increased risk of cancer may be weighted to a greater or lesser extent insofar as the following criteria are met:

(1) Definition of Study Population. A clear description is made of the population from which the study group was selected, the method of selecting the subjects of the study group, the criteria and rationale for inclusion or exclusion of study subjects and the procedure and rationale by which the study subjects were classified according to presence or absence and degree of exposure.

(2) Reference Population. A clear description is made of the reference or standard population against which the study group is contrasted and the procedure and rationale for selecting that reference or standard population.

(3) Disease Ascertainment and Classification. A clear statement is made of the specific procedures and sources for disease ascertainment including the degree of completeness of that ascertainment for the study and the reference population. The criteria are specified for classification of morbidity and mortality (e.g., nosology) and a statement is made addressing the comparability of study and reference population regarding the classification scheme.

(4) Positive or Negative Bias or Confounding. As the operation of factors in the study design or execution may lead erroneously to an observed excess or deficit of cancer risk among exposed individuals, a clear statement is made of the magnitude of over- or underestimating disease risk in the study group. Such factors to be considered are selection of healthy individuals for work and ethnicity and life-style differentials.

(5) Dose-Response Relationship. A dose-response relationship is demonstrated, that is an increase in cancer morbidity or mortality with an increase in degree of exposure. Demonstration of such a relationship provides strong evidence for incriminating the agent under study as a causal factor in the etiology of cancer causation. However, because of difficulty in the quantification of actual degree of exposure (dose-rate, deposition, retention, excretion), such a relationship may not always be apparent. For that reason the lack of a demonstrated dose-response relationship may not negate the carcinogenicity of an agent.

In addition to these criteria, it must be recognized that any epidemiologic study will have confidence limits around estimates of association or relative risks (e.g. around Standard Mortality Ratios, etc.). As pointed out below, in a study reported as non-positive or "negative", the upper confidence limit may fall at a relative risk considerably above unity

and thus the study cannot be regarded as decisively negative but only as excluding a relative risk that is above the upper limit. Finally, a non-positive epidemiologic study may be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elasped since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years.

A concise summary of the nature of epidemiology and of the principal types of study that are undertaken was presented in an exhibit to the Record:

"Epidemiology is concerned with identifying patterns of distribution of diseases that occur in man. Rates of incidence and mortality are reviewed in the context of time trends, geography and personal characteristics. This descriptive profile of a disease serves to guide the pursuit of etiologic factors that are likely determinants of a specific pattern.

"The epidemiologic methods that are concerned with testing causal hypotheses can be classified either as case-control or cohort in type. The case-control ('retrospective', 'case history') study is most suitable in studies of rare diseases, in 'fishing' for multiple factors of uncertain significance and for the initial exploration of a specific etiologic hypothesis. The cohort ('prospective', 'longitudinal', 'follow-up') study is advantageous in that it provides a direct measure of the incidence or risk of developing a disease in individuals with a specific characteristic, and is most suitable for testing a particular hypothesis, which has already been developed from prior retrospective (and/or cross-sectional) studies. For practical purposes, the various caveats about sample size in cohort studies guide the epidemiologist to focus on hypotheses that involve a relatively common exposure (in more than 2 or 3% of individuals at risk), a relatively common cancer (incidence of 1/1000/year) and for discerning relative risks (risk ratios) in the exposed that are at least twice that of the control group." (Schottenfeld *et al.*, 1978, p. 5; Hearing Exhibit 219)

Another definition in a standard textbook emphasizes that epidemiology has both descriptive and analytic aspects:

"Epidemiology is the study of the distribution and determinants of disease prevalence in man * * *

"* * * Two main areas are indicated in the definition. These are the study of the distribution of disease (descriptive epidemiology) and the search of determinants of the noted distribution (analytic epidemiology). The first, describing the distribution of health states in terms of age, sex, race, geography, etc., might be considered an extension of the discipline of demography to health and disease. The second, involving interpretation of the distribution in terms of possible causal factors, is the special contribution of epidemiology. Definitions of epidemiology that consider only the descriptive phase do not indicate the unique component of the discipline". (McMahon *et al.*, 1970, p. 3) (Footnote omitted)

3. Strength and Importance of Epidemiologic Data

The overwhelming importance of epidemiologic data is that they provide direct evidence of associations between exposure to chemicals and patterns of disease *in humans*. Thus, when a relatively clear positive association is demonstrated in an adequately conducted study, its relevance to the prediction of human hazards and risks is clear and unmistakable: there is usually no room for the lengthy debates that inevitably accompany attempts to extrapolate from experimental results in animals to predict human hazards or risks. Dr. Hoover (NCI) discussed the strengths of the epidemiologic method at some length in his written statement:

"The strengths of the epidemiologic method are twofold. First of all, this method allows the direct measurement of the risk of cancer due to an exposure in a *human* population. It can thus identify causes of cancer in humans that are associated with intermediate or high levels of risk. Secondly, there is a much less obvious role and strength of the epidemiologic method. That is, these kinds of studies can allow someone to gain insights into the basic mechanisms of a disease causation (for cancer the mechanism of carcinogenesis)." (Hoover, S. 11)

Dr. Hoover later described an appropriate use of epidemiology as one which identifies hazards associated with exposure to a risk factor, and allows insights into mechanisms of these associations such as "latent period related to potency" and "susceptibility by age-at-exposure" (Hoover, S. 16). In his oral testimony, Dr. Hoover (NCI) stated that epidemiology is:

"* * * an extremely important tool in identifying occupational exposures and other hazards because it studies people in the context in which they are exposed. So it identifies excess risk that might have been missed in studying pure exposures." (Hoover, Tr. 793)

Dr. Bo Holmberg (Swedish NBOSH) made a similar point:

"Epidemiological studies are the only types of studies which, under ideal conditions, can give numerical estimates of the excess risk of getting cancer in workers' populations. Experimental studies with animals can presently not give precise information on the quantitative risk of human exposure. Thus, it is important to carefully analyze populations at risk." (Holmberg, S. 6)

Several references from the literature introduced into the Record support the importance of consideration of positive epidemiological data. Sir Richard Doll stated that, of all the agents known to cause cancer in the workplace, most were initially discovered by observation in humans (Doll, 1977; Annex E to Peto statement). Dr. Lorenzo Tomatis (IARC) cited the examples of the aromatic amines and bis(chloromethyl)ether as two chemicals for which the cancer hazard in humans was demonstrated epidemiologically long before positive animal data were generated (Tomatis, 1977b, Appendix 4 to Tomatis statement).

On the other hand, some witnesses looked upon epidemiologic evidence primarily as a method for verifying the results of animal testing. They cited the statement of the Second Task Force for Research Planning in Environmental Health as follows:

"Epidemiologic investigation can be of value in the development of an understanding of chemical carcinogens in two major areas which are in urgent need for exploration: (a) Many chemicals exist which have an important bearing on current lifestyle but which, subsequent to their general use, have been shown to introduce cancer in laboratory animals. DDT is a case in point. In such cases, it should be possible, on a world and/or national basis, to define populations that have been extensively exposed during manufacture and use of specific agents. The cancer morbidity or mortality of these populations could provide valuable evidence for the validity of certain animal test systems as predictors for human cancer." (DHEW, 1977, pp. 285–286; Reference 25 to Robinson Statement)

One of the more persuasive statements on the importance of epidemiology came from Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska) who stated:

"* * * clear epidemiologic data in humans does not require a delay of regulatory action while a suitable animal species is identified and a test conducted. Most agents known to be carcinogenic in man have been identified in the first instance by case reports and epidemiologic studies and have subsequently been confirmed in animal studies as carcinogens." (Shubik, S. 12)

An earlier discussion of the uses of epidemiology emphasized its importance in application to prevention of disease:

"The main function of epidemiology is to discover groups in the population with high rates of disease, and with low, so that causes of disease and of freedom from disease can be postulated. The most obvious and direct examples are the original observations on the nutritional deficiencies (scurvy, beriberi, pellagra, goiter); the geographical study of

cancer (especially of the skin and liver); the industrial cancers (bladder, for instance); and industrial accidents (of coal-miners or railway workers). The biggest promise of this method lies in relating diseases to the *ways of living* of different groups, and by doing so to unravel causes of disease about which it is possible to do something."

* * * * *

"The great advantage of this kind of approach to prevention is that it may be applicable in the early stages of our knowledge of diseases, to disrupt the pattern of causation before the intimate nature of diseases is understood. Sufficient facts may be established for this by epidemiological methods alone, or in combination with others. The opportunity may thus offer to deal with one cause, or with various combinations of causes. Moreover, the possibility of two types of control may be opened up—environmental (as in the fluoridation of water) and personal (through alteration of diet and hygiene)." (Morris, 1955, p. 399) (emphasis in original)

In the context of this rulemaking, this statement emphasizes how epidemiologic studies can lead to preventive measures (i.e., reduction in exposures), even before the causal associations are fully worked out. This is another respect in which epidemiologic studies offer important advantages over experimental animal studies.

Dr. David Wegman (Harvard Univ.) made a concise statement of the importance of epidemiology in elucidating occupational cancer risks:

"Epidemiology can prove a powerful tool to evaluate risk in occupational settings. Although it alone has not been responsible for many of the discoveries of occupational cancer risk, it has proven very useful in confirming risk or characterizing its extent. In fact, it is a tool which has been underutilized in the evaluation of work related cancer risks either due to poor applications or to missed opportunities." (Wegman, S. 7) (Footnote omitted)

4. Limitations of the Epidemiologic Method

Dr. Hoover (NCI) discussed some of the major weaknesses of the epidemiologic method:

"There are at least five major weaknesses to the epidemiologic approach. First of all, as you may have inferred from my emphasizing that epidemiology was reasonably strong in identifying intermediate and high levels of risk, it is quite weak at identifying the causes of very low levels of risk. Very small differences in risk between a group exposed to some substance versus that in a group not exposed to it could be due to a variety of reasons: for example, chance, or other differences between the exposed and unexposed which we either do not know about or cannot adequately control for. Because of this, it becomes next to impossible to say with any assurity that a very low level of risk is caused by a similarly low level exposure to some substance. What do I mean by low level of risk? I believe I can put this in context by noting that the lowest excess cancer risk that I know of that is directly observable in a group of exposed individuals and is generally accepted as being due to that exposure and not some other factor, is the 30% excess risk of childhood leukemia among children who were exposed to radiation *in-utero* in the last trimester of pregnancy (pelvimetry). Indeed, it has taken us some 20 years to become reasonably convinced of this 30% excess risk.

"The second weakness of the method, and perhaps its most important weakness, is what is referred to as latent period or induction-incubation period. This is the interval between exposure to a cause of a disease and the actual manifestation of the disease itself. As you are all aware, for cancer causing exposures these latent periods are quite long—from 5 years to over 50 years.

"The third weakness of the method is in its lack of specificity of exposure. Often, in fact usually, we epidemiologists are studying the effect of exposure to mixtures of chemicals or other agents, rather than pure exposures to a single toxic substance.

"The fourth weakness is the inability to control for unknown risk factors for the disease in question. In an experiment the randomization procedure hopefully introduces some control for unknown factors. In observational studies, we can control for known confounding factors, but obviously cannot guarantee control for unknown confounders.

"The last weakness of the approach encompasses the practical problems involved in doing epidemiology. In order to effectively function, an epidemiologist needs to have access to appropriate information on large groups of people. Sometimes this is possible, and sometimes the information just does not exist. In addition, there is currently a lack of enough competent epidemiologists even to evaluate adequately the information that does exist." (Hoover, S. 11–12)

Many witnesses believed that a major problem with retrospective epidemiologic studies is the identification and quantification of exposure of workers to hazardous agents. Dr. David Wegman (Harvard Univ.) stated:

"First and foremost is the problem of defining exposure. Most of the existing epidemiology studies on occupational cancer rely on retrospective methods. Industry, however, as a rule had not kept much let alone adequate environmental data on workplace exposures. Many studies therefore have had to use duration of employment as a measure of exposure rather than any direct measure. This problem has led to no end of controversy about the interpretation of results from these studies and rightly so. Even when attempts are made to estimate past exposures, the estimates are gross and problematic. On the other hand, if one were to accept duration of employment with all its shortcomings, many companies do not maintain records appropriate to such use. This gives special meaning to the somewhat whimsical definition of an epidemiologist as a scientist in search of a denominator. Studies of work related cancer too often must be planned where appropriate records have been maintained rather than where exposure or use circumstances would indicate the need or desirability for evaluation.

"Even in these instances records are a problem. There may be inadequate duration of employment to create sufficiently distinct groups of duration when duration is an indirect measure of dose. There may further be inadequate length of time since exposure to provide enough time for tumors to present themselves." (Wegman, S. 7)

Discussing the data on asbestos, one of the best-studied human carcinogens, Dr. William Nicholson (Mount Sinai School of Medicine) stated:

"In all of these [studies] we have limited dose data. There is scant information on exposures to insulation workers. In 1945, there was one paper published using techniques no longer considered adequate of insulation exposures in naval shipyards. Other than that, the only data which really exists is that obtained in the last eight to ten years. So that to obtain a dose-response relationship for asbestos, one of the most [studied] carcinogens, we are very limited; and for many others the limitation is even greater. In fact, if one looks at the two dozen known human carcinogens, only three or four exist that have data that would allow some estimate of past exposure." (Tr. 1708–1709)

Mr. Richard Waxweiler (NIOSH) stated that another problem is that records of past exposure are often not available:

"Another problem that makes it extremely difficult to do epidemiology in a retrospective sense is that there is—just the fact that we quite often cannot get the records to look at these exposures, to look at who has worked in certain areas in the past. There is no legislation that I know of today that says we have to maintain personnel records on people exposed for the last 30 or 50 years, given in the absence of a recognized hazard." (NIOSH, Tr. 2952)

Specificity of exposure often cannot be determined, as stated by Dr. Bo Holmberg (Swedish NBOSH):

"Epidemiological studies are often difficult to make conclusive with respect to specific agents, because it is seldom possible to isolate a single variable in the study. Humans are exposed to many chemical agents in their work environment and in the general environment. In many cases it is not possible to establish a causal relationship between an excess frequency of cancer and exposure to a single chemical. In those cases one can only define a risk group with reference to specific technological processes, plants, companies, or industrial branches." (Holmberg, S. 8)

In addition, there are the problems associated with job mobility as pointed out by Dr. Francis J. C. Roe (AIHC):

"In a rapidly changing situation, workers tend to be exposed to a particular chemical for no more than a few years before the

process or product becomes obsolete or the worker moves to another job. The effects of even a potent carcinogen might therefore be (a) minimised and (b) overlooked. The effects are apt to be overlooked because, in man, a latent period of several years tends to separate start of exposure to a carcinogen and any discernible increase in cancer risk. If during the latent period a worker moves on to other employment, the association between his development of a cancer and his exposure to the agent which contributed to its cause will be more difficult to discern.

"The briefer the period of exposure to a carcinogen the longer the latent period is likely to be and the more unlikely it is that the association will be recognized. Modern technology enables large amounts of particular chemicals or products to be produced by very few people. In these circumstances it might be difficult to recognise the effects of even a relatively potent carcinogen, particularly if the type of cancer hazard involved occurs commonly in unexposed people.

"During his working life-time a worker in, for instance, the chemical or drug industry might be exposed simultaneously or sequentially to many different suspect chemical agents. In these circumstances it might be very difficult to recognise the one agent out of the many that was primarily responsible for increasing the risk of his developing cancer." (Roe, S. 9–10)

The problem of defining exposure has sometimes been dealt with by indirect means—the utilization of job titles to specify exposure groups. But this also results in problems:

"There are many specific problems making occupations difficult to study. Many workers are unaware of the conditions surrounding them or the substances they handle. The latter difficulty often results because a particular agent is known by a trivial chemical or trade name. Many persons change occupations from time to time, and may forget or lose interest in the experiences of former occupations. Further difficulties result because many occupational titles have no specific exposure connotation—a single title may refer to occupations involving exposure to very different substances; equally problematič, a particular exposure may be sustained in occupations with dissimilar titles or duties. The value of occupational titles as an index of exposure is further reduced by their upward social drift, particularly on death certificates. These difficulties are vexing in case-control studies, which are dependent on memory, and in any study that uses titles rather than descriptions of duties or exposures to categorize occupations. Such studies, especially when negative, are not persuasive." (Cole and Goldman, 1975, p. 169; Exhibit to Squire Statement)

Even after obtaining reasonable estimates of exposure, the results of an epidemiologic study are not necessarily relevant to other exposed populations, because of the effects of other, unknown risk factors. As Dr. Hoover (NCI) stated:

". . . you would have some sort of estimate of the bounds of the potential risk, but you would also have to realize that that applies only to this kind of population exposed over that period of time. And if the population you were wanting to extrapolate to smoked differently, smoked lower tar cigarettes, higher nicotine cigarettes, ate a different diet, were exposed to a different mix of chemicals in the environment, you may indeed get a different estimate, that it is extrapolatable to people who were exposed in that manner for that duration of time at that level." (Hoover, Tr. 794)

It may be noted that this comment applies specifically to the quantitative extrapolation of risk from one group of workers to another group. The existence of other risk factors would not ordinarily limit the qualitative extrapolation of hazards.

In his written testimony, Dr. Hoover (NCI) illustrated the fact that similar effects on cancer incidence could also be due to different types of exposure:

"A case in point is bladder cancer, the tumor perhaps most closely linked to occupational exposures. It has been estimated that 20% of the bladder cancers that occurred in the Boston metropolitan area at one particular point in time could be attributed to occupational exposures. The same estimate was computed for Leeds, England, and New Orleans, Louisiana at particular points in time. Before one jumps to the conclusion that in general 20% of bladder cancer is occupational, it should be realized that many of the industrial exposures occurring in each of these areas did not occur in the others. For example, in the Boston metropolitan area, very little of the bladder cancer could be attributed to exposures in the organic chemical industry which may be responsible for the higher percentage of occupational induced bladder cancer in Salem County, New Jersey (16,21)." (Hoover, S. 7)

Some known risk factors or confounding variables which may affect the interpretation of an epidemiologic study include:

a. *Socioeconomic status:*

"Finally, a problem results because occupation is so closely related to social class. Indeed, in many studies occupational level—not exposure—is used to designate an individual's social class. Social class, in turn, is a correlate of risk for many cancers, including some for which the association is quite strong. The possible confounding by social class and other characteristics (e.g. race) of an employed group should be evaluated before it is inferred that a causal association exists between the occupational exposure and a cancer. For example, soft-coal miners were reported [8] at increased risk of cancer of the stomach, but when the effects of social class were evaluated [9], the association was much reduced." (Cole and Goldman, 1975, p. 169; Exhibit to Squire Statement)

Associations between cancer incidence and social class were also discussed by Dr. Francis J. C. Roe (AIHC) (S. 12–13). Mr. Richard Peto (Oxford Univ.) also pointed out that errors in reporting cancer incidence result from inadequate autopsy procedure and diagnoses, especially for lower class persons (S. 11–14). Dr. Johannes Clemmesen (Danish Cancer Registry) also referred to social class effects (S. 5).

b. *Age at exposure:*

"Another potentially interesting item, since it could have profound implications for prevention, is the relationship of excess risk to age-at-starting exposure. In one study [12], all the excess risk of bladder cancer among men with occupational exposures was confined to those whose exposure began prior to age 25. If this finding were confirmed, it would have considerable significance. Studies of occupational carcinogenesis are needed to determine the relationship of excess risk to age at first exposure. At least two issues appear involved: First, younger persons might be more susceptible to cancer induction; and second, only persons who are first exposed while young may work long enough to sustain carcinogenic exposures. (The latter explanation did not apply in the bladder cancer study cited.) In either case, the implication is that only persons, say, 40 and over should be placed in the possibly carcinogenic work environments. Yet, on the basis of existing knowledge, we cannot make this recommendation. Several studies [13,14] suggested that elderly persons are actually more susceptible than the young to cancer induction. These relationships should be worked out in detail so that their preventive implications can be exploited. It may be that both the young and the old are susceptible, but that the middle-aged are relatively resistant to carcinogenesis." (Cole and Goldman, 1975, p. 170; Exhibit to Squire Statement)

c. *Smoking history:*

Smoking history should generally be controlled for in epidemiologic studies because of the major influence of smoking on cancer rates at several sites. Dr. Irving Selikoff (Mount Sinai School of Medicine) presented data on the effect that smoking has on the incidence of lung cancer in asbestos insulation workers. From a study population of 17,800 people, 2,066 men did not smoke cigarettes while 9,591 reported that they had a history of cigarette smoking:

"* * * few lung cancers were seen among those with no history of cigarette smoking, only eight. On the other hand, among the 9,500 men with a history of cigarette smoking, there were 325 deaths of lung cancer. The same was true of esophagus, with a significant increase only among those with a history of cigarette smoking.

* * * * *

"We found that among the 2,066 non-cigarette smokers there should have been 1.82

deaths, the way the statisticians put it, 1.82 deaths of lung cancer. There were eight. In other words, somewhere around four to five times as many. But this is certainly not a major public health problem. You had four times or five times the number of a very small number; and five times nothing is still not very much.

"On the other hand, you had again five times the already high risk of cigarette smoking, so that instead of 67 deaths anticipated, 325 actually occurred, confirming not simply the carcinogenicity of asbestos in terms of lung cancer among those exposed, but also the extraordinary multiple factor etiology.

"Now, what does this mean? Taken with other data that Dr. Nicholson has used, it suggests that this one carcinogen has been responsible for an extraordinary number of deaths and may be anticipated to be responsible for this in coming years, at least for the next thirty to forty years, as a result of our past inadequacies." (Selikoff, Tr. 1699, 1702)

E. Cuyler Hammond in a chapter of *Persons at High Risk of Cancer* also commented on the influence smoking has on the interpretation of epidemiologic data:

"The relationship between cigarette smoking and cancer may be illustrated by a prospective epidemiological study of over one million men and women who were enrolled between October 1, 1959; and March, 1960, and traced through September 30, 1965 [7,8]. The findings are consistent with dozens of other studies conducted by many different investigators in many different countries. Mortality ratios for cancer were computed by dividing the age-standardized death rate of cigarette smokers by the age-standardized death rate of those who never smoked regularly (Table 1). Cigarette smoking increases the risk of lung cancer to a greater degree than any other cancer site. In addition, cigarette smoking (as well as pipe and cigar smoking) multiplies the risk of cancer of the buccal cavity (lip, mouth, and tongue) and pharynx by a factor of about three to ten depending upon the type and amount of smoking. It is hard to estimate the mortality ratio with any precision because the rate in nonsmoking men in the United States is very low. As shown in several studies, heavy drinking of alcoholic beverages increases the risk of mouth and throat cancer even further in smokers [9].

"Furthermore, cigarette smoking greatly increases the risk of cancers of the larynx and esophagus. Again the rarity of these cancers in non-smoking American men makes it difficult to estimate the exact degree of risk in terms of mortality ratios. Smoking also multiplies the risk of bladder cancer, particularly among men under the age of 65. This finding has been confirmed by many studies and appears beyond dispute.

"The increased risk of cancer of the pancreas in cigarette smokers is supported by histologic evidence. Atypical changes have been observed in the nuclei of pancreatic duct cells among smokers coming to autopsy, with the extent of such changes increasing with the amount of smoking [10]. The relation of smoking to cancer at other sites is less definitely established. In several studies, for example, deaths ascribed to liver cancer have occurred more frequently in cigarette smokers than nonsmokers [1]. However, in many cases, there is considerable doubt as to whether the liver was the primary site of cancer. The association may be due to lung cancer with liver metastases being mistakenly reported as primary liver cancer. This subject is worth further investigation." (Hammond, 1975, p. 182; Exhibit to Squire Statement)

d, Errors in reporting.

Dr. Douglass Lloyd (Connecticut Dep't. of Health) pointed out the limited reliability of death certificates:

"* * * it depends on how the death certificates are filled out. The death certificates may list everything from heart failure for someone who had an underlying neoplastic process which resulted in pulmonary obstruction and led to a respiratory cardiac failure. I do not think you can say that if there is no higher incidence it necessarily rules out a carcinogen having an effect on the population you are looking at compared to the general population." (Lloyd, Tr. 8020; see also Peto, Tr. 2543)

This factor, as well as others, may act to bias or distort the data and thus result in problems in evaluation.

e. Problems in identifying weak associations.

A recent review of epidemiologic studies relevant to evaluating the risks posed by saccharin, conducted by the National Academy of Sciences' Committee for a Study on Saccharin and Food Safety Policy, provided a synopsis of the factors that can complicate the interpretation of studies which are designed to detect weak associations.

"Three types of epidemiologic studies are reported in this chapter: time-trend studies, prospective studies, and retrospective case-control studies. All three studies were designed to determine whether there is a higher probability (or risk) of bladder cancer with exposure to saccharin than in its absence. The methods and results of these studies illustrate the difficulties that are encountered with epidemiologic data.

"First, many of the studies were originally conducted for purposes that are unrelated to the present goal of determining the association, if any, of saccharin use with bladder cancer or other health effects. These studies rarely have detailed information on saccharin consumption because their purpose was to investigate other factors associated with bladder cancer such as cigarette smoking or coffee drinking.

"*Second, investigations of this relationship are designed to detect a strong association if it exists, but they may include too few study subjects to measure a weak one.* Since the number of persons using saccharin is so great, even weak associations are important in predicting risks to health.

"Finally, with the most competent design and with adequate numbers of subjects to identify weak associations, an investigator will often be unable to distinguish the expected association from the confounding effect of some other factor. Such variables can be excluded by appropriate study design when the factors are known in advance. Since unknown factors cannot be formally excluded, it is ultimately a matter of judgment whether an association that persists after ruling out all known confounding factors should be accepted as causal. *If the persisting association is strong, e.g., a tenfold or greater increase in a disease risk, it is difficult to defend the position that an unsuspected factor may be responsible. However, if the persisting association is weak, e.g., less then a twofold increase, such an unsuspected variable may indeed be responsible.* Cigarette smoking or hazardous occupations may be variables that confound low-level associations between saccharin use and the occurrence of bladder cancer. Ultimately, a weak association may be demonstrated by intervention studies, clinical trials, or prophylactic trials. There have been no intervention studies of saccharin. Consequently, the interpretation of any results must be judgmental at present."

* * * * *

"The relationship between saccharin and disease risk has been examined mostly through case-control studies of bladder cancer (Howe *et al.*, 1977; Kessler, 1976; Kessler and Clark, 1978; Morgan and Jain, 1974; Simon *et al.*, 1975; Wynder and Goldsmith, 1977). The exception is the above-mentioned study of spontaneous abortion (Kline *et al.*, 1978). In all of these studies, the saccharin exposure information has been obtained by questionnaires with known shortcomings such as biased response due to differential recall and interviewer bias in the assessment of exposure."

"Assuming that saccharin is a carcinogen of low potency in humans and that it produces a risk as low as that suggested by Howe *et al.* (1977), the numbers of bladder cancer cases studied have been too small (Kessler, 1976; Simon *et al.*, 1975; Wynder and Goldsmith, 1977) to demonstrate a statistically significant difference. Furthermore, the cases were often matched with controls but matching was ignored in the analysis (Kessler, 1976; Simon *et al.*, 1975; Wynder and Goldsmith, 1977). This may result in an underestimate of the actual risk."

"Since the respondents' medical status could be easily distinguished (or was known by the questioner), the possibility of interviewer bias exists in all retrospective questionnaire studies without an independent assessment of exposure. For example, the interviewer may have tried to "coax the desired response" from the cases with more enthusiasm than he or she portrayed to the controls. This criticism can be made of any study that is built on personal interviews and has been mentioned by the FDA/NCI Interagency Saccharin Working Group (USDHEW, 1977) in a critical review of Kessler's study (Kessler, 1976; Kessler and Clark, 1978)."

* * * * *

"Synergy should be addressed (Hicks and Chowaniec, 1977; USDHEW 1977) when considering multiple exposures among

saccharin users. Such exposures are likely to include cigarette smoking, coffee drinking, and a history of hazardous occupational exposure."

"Latent times for malignancy are commonly measured in decades, and periods of 30 to 40 years may be required for the total effect of any carcinogen to become apparent in humans. A common problem of all the studies on humans to date is that the major increase in use of saccharin may be too recent for its carcinogenic effects, if present, to be manifest." (NAS, 1978, pp. 3–80–81, 3–89, 3–92, emphases added)

Other confounding factors discussed in this Committee report—selection bias, recall bias, coffee consumption, medical history, social status and type of water supply—are less likely to be significant in occupational studies than in the case-control studies reviewed by the Committee. In any case, such biases and confounding factors are only likely to be important when relative risks are small—i.e. when the survey shows only a weak correlation with exposure to a substance, or no association at all. The important point made by the Committee is that *these confounding factors and biases are unlikely to negate a study which shows a strong positive result.* Thus, there is a crucial difference between the interpretation of positive and negative studies: studies that show no association, or only a weak positive association, need scrupulous review to exclude the possibility of confounding factors, whereas studies that show a strong positive association can be accepted even if the possibility of minor biases cannot be excluded. This point was also made directly by Dr. Hoover (NCI) (S. 11).

API also presented an informative summary of problems involved in evaluating epidemiologic studies, especially in the occupational situation.

"The methodological features of epidemiological studies of the workplace and cancer are reviewed in Table I. The important parameters include the type and "strength" of exposure, age at initial exposure, latency or the frequency distribution of the interval from first exposure to the initial diagnosis of disease, duration of exposure, intensity of exposure and its variability over the cumulating person-years at risk and the spectrum of morbidity and mortality. In addition to the methodological issues summarized in Table I, there are other interpretive pitfalls in epidemiological research that may confound or obscure precise inferential reasoning.

"Confounding refers to the extraneous influence of factors, other than the measured occupational experience, on the association with the risk of cancer. For example, social class is closely linked with occupational status, and may be more directly associated with the risk of developing or dying from various types of cancer. Social class factors may be linked with personal habits, aspects of life style that include patterns of nutrition and non-occupational environmental factors, and access to and utilization of medical care services. The observed increased risk of cancer may arise from mixed chemical and physical exposures or the interaction of occupational and non-occupational factors.

"The observations emanating from epidemiological studies may be suspect because of lack of accurate exposure data and limited or incomplete follow-up from the onset of some remote exposure, even if it was of short duration. In the studies that depend upon recall, the workers may be unaware of the identity of the substances that they have handled. Routine records rarely satisfy the needs of epidemiological research, but rather what may be needed is the development of a standardized comprehensive occupational health information system with prospective monitoring throughout a defined work force. Job titles may not connote a specific exposure, or the same title may encompass a multitude of possible toxic agents that are likely to produce a variety of effects. Each individual worker may have moved through a number of different jobs even within the same manufacturing industry. The task is to attempt to group the various jobs into homogeneous categories of exposure." (Schottenfeld *et al.*, 1978, p. 6; Hearing Exhibit 219)

Table I—*Methodological Features of Occupational Studies*

[From Schottenfeld et al. 1978]

Issue	Commentary
"1. 'Signal' cancer.....	Suspect an occupational agent when cancers of uncommon site or histology appear in space-time clusters, particularly when some cases are diagnosed under age 60 years (e.g. mesothelioma, pleura and peritoneum (asbestos) angiosarcoma, liver (vinyl chloride monomer) adenocarcinoma, nasal cavity and paranasal sinuses (isopropyl oil, chromium, nickel, woodworkers in furniture industry, boot and shoe workers) squamous carcinoma, scrotum (soot, lubricating oils) oat cell carcinoma, lung (Bis chloromethyl ether, chloromethyl methyl ether) acute leukemia including erythroleukemia (benzene, rubber workers) osteogenic sarcoma (radium watch dial painters)).
"2. Interval since onset of exposure	The latent period between first exposure and onset of disease may vary between 5–40 years. The calculation of latency or the median interval of time of onset of disease, and the approximate confidence limits about the median, should be corrected for the spontaneous incidence of cancer, particularly for the more common types of cancer and for relative risks less than 4.0. Factors that may influence latency include the type and strength of exposure, age at first exposure, interaction with mixed or multiple chemical exposures (including cigarettes) and individual (host) factors. The instantaneous risk of disease or death may not be constant over time and, therefore, a life table analysis may be more appropriate than cumulating person-years of experience, irrespective of the time since first exposure.
"3. Dose-response relationship.....	Unfortunately crucial retrospective dose data are often not available. The dose-rate may have varied over time, therefore duration of exposure may not be equivalent among workers unless interval exposure levels, duration and age are considered concomitantly. There are methods to summarize linear and nonlinear components of the dose-response relationship.
"4. Synergism:	Is the risk associated with a particular exposure additive or multiplicative (interactive) with known causes of the disease? Examples of interactions between known causes of the same disease are few in the epidemiologic studies of occupational carcinogenesis (e.g., cigarette smoking in asbestos workers or uranium miners). Further research is needed on this important issue, for example, with respect to cigarette smoking and known occupational causes of lung and lower urinary tract cancers. Demonstration of synergism has important implications for industrial hygiene, selective screening and counseling of individual workers.
"5. Why not use the general population as the only control group in a cohort study?.....	Although most cohort studies of occupational mortality use the general population as a standard for deriving the expected number of deaths, pre-employment selection ("healthy worker" bias) affects the comparative experience. Age-standardized mortality ratios (SMR) [The standardized mortality ratio (SMR) has been widely used in occupational studies for the evaluation of overall and cause-specific mortality. It is derived from the ratio of observed number of deaths to those expected based upon the age, sex, race, geographic area, calendar period, cause-specific mortality of a standard population. An SMR of less than 100 indicates that for the aggregate of person-years there were fewer deaths than expected, while an SMR above 100 implies the opposite. The SMR, which is distinctive from a summary estimate of relative risk, has been evaluated critically in recent years.] in general are 60 to 90 percent of the standard in the working population. The selection factors are particularly in evidence when reviewing mortality due to cardiovascular, chronic respiratory and infectious diseases, but less striking for malignant neoplasms. The effect is higher in the employed blacks. A suggested remedy is to develop reference working populations from other published cohorts of workers, a 10 percent sample of social security recipients (Longitudinal Employer—Employee Data File), and/or internal comparisons within the study cohort stratified by degree of exposure, age, sex, race, geographic area of residence and tobacco smoking history." (From Schottenfeld *et al.*, 1978; Hearing Exhibit 219)

Another witness for API, Dr. Peter Goldman, (Harvard Univ.) placed strong emphasis on the insensitivity of epidemiological studies:

"Our concern increases when we consider the insensitivity of our methods for identifying an association between a chemical exposure and human cancer. Generally this association has only been made when an increased incidence of a tumor of an unusual type was noted or when an unusual clustering of a common tumor occurred in a particular population. Unless specific epidemiological information is available for analysis and there is reason to suspect a particular result, even a moderate increase in a common tumor may escape detection.

"It would also be worrisome to rely exclusively on truly prospective epidemiological studies because there is often a latent period of several years between the time of exposure and the development of clinical cancer. Thus relying on an early warning system based on the appearance of a few human cases could mean that the signal indicating a need to modify exposure could come too late to protect a large population already exposed.

"Detection of human cancers by epidemiological surveillance is further hampered by the mobility of the American work force. Thus even if traditional epidemiological methods are applied in an improved manner they, considered alone, may still not offer satisfactory protection against cancer that may be caused by occupational exposure." (Goldman, S. 3–4)

A final limitation of epidemiologic studies is that for most chemical substances and industrial processes, relevant data are lacking simply because such studies have not yet been conducted. Dr. David Rall (Director, NIEHS) commented upon this deficiency, citing a review by Tomatis, *et al.* (1977):

"In the first place, [the estimates of the fraction of cancers caused by occupational factors] are based only upon the *known* examples of occupational carcinogens. As other witnesses who are specialists in cancer epidemiology have pointed out, definitive epidemiological studies are very difficult to carrry out (because of the long latent periods for development of cancer, among other factors). Even in occupational settings only the stronger carcinogenic agents are likely to be detected. More important, only a limited number of occupational exposures have ever been investigated for carcinogenic risk. Attached as Appendix G to this statement is a paper by L. Tomatis *et al.*, describing the program of the International Agency for Research on Cancer (IARC) in which monographs are prepared and published on potential carcinogens. In the first 16 volumes of the monographs, 368 substances have been evaluated. The chemicals were selected on the basis of two criteria: (a) that there was evidence of human exposure and (b) that there was some evidence of carcinogenicity in experimental animals and/or of a human risk. Among the 368 substances were included 173 industrial chemicals, 5 industrial processes, and 2 industrial by-products; occupational exposure can be inferred for at least 336 substances (90%). Twenty-six chemicals or industrial processes were identified as associated with an excess carcinogenic risk to man (Table II in Appendix G) and for a further 221, some evidence of carcinogenicity in one or more animal species was found. For the majority of these 221 chemicals evidence of human exposure exists but no evaluation of the carcinogenic risk to man was made, either because no epidemiological studies or case reports were found (205 compounds), or because the results were inconclusive (16 compounds). For the remaining 121 chemicals, the available studies were inadequate to make an evaluation of the presence or absence of a carcinogenic effect (pp. 9–10 of Appendix G). Thus, of the 368 compounds reviewed in the IARC monographs, less than 8% had received adequate investigation to judge whether or not they have carcinogenic effects in humans. This is a grossly inadequate basis on which to assess the percentage of human cancers 'caused' by occupational exposure." (Rall, S. 3–4)

Dr. Irving Kessler (Johns Hopkins Univ.) made a similar point and added that studies conducted to date with occupational groups have been deficient in quality as well as quantity:

"In fact, there have been relatively few controlled epidemiological studies of occupational groups. Rather, the large majority of human studies have been conducted upon hospitalized patients with and without a given disease. Only in the last few years, with the emergence of interest in occupational health hazards, have occupational studies been undertaken by epidemiologists. With a few exceptions, most of these could not, until recently, have been classified as well designed and controlled epidemiological studies. This is an emerging and very important field where methodologic approaches are still being developed." (Kessler, S. 9)

5. Criteria for Evaluating Positive Epidemiologic Studies

A number of participants and exhibits discussed criteria or guidelines for the establishment of a causative relationship between exposure to an agent and increased incidence of cancer. For example, the International Agency for Research on Cancer (IARC) presented the following criteria in the most recent revision of the preamble to its Monograph series:

"An analytical study that shows a positive association between an agent and a cancer may be interpreted as implying causality to a greater or lesser extent, if the following criteria are met:

(1) There is no identifiable positive bias.

(By positive bias is meant the operation of factors in study design or execution which lead erroneously to a more strongly positive association between an agent and disease than in fact exists. Examples of positive bias include, in case-control studies, more nearly complete ascertainment of exposure to the agent in cases than in controls and, in cohort studies, more nearly complete detection of cancer in individuals exposed to the agent than in individuals not exposed).

(2) The possibility of positive confounding has been considered.

(By 'positive confounding' is meant a situation in which the association between an agent and a disease is rendered more strongly positive than it truly is as a result of an association between that agent and another agent which either causes or prevents the disease. An example of positive confounding is the positive association between coffee consumption and lung cancer, which results from their joint association with cigarette smoking).

(3) The association is unlikely to be due to chance alone.

(4) The association is strong.

(5) There is a dose-response relationship.

"In some instances a single epidemiological study may be strongly indicative of a cause-effect relationship, however, the most convincing evidence of causality comes when several independent studies done under different circumstances result in 'positive' findings." (IARC, 1978, Vol. 17, p. 18).

IARC does not usually consider case reports or descriptive epidemiologic studies to be sufficient in themselves to establish a causal association:

"Evidence of carcinogenicity in humans can be derived from three types of study, the first two of which usually provide only suggestive evidence: (1) reports concerning individual cancer patients (case reports), including a history of exposure to the supposed carcinogenic agent; (2) descriptive epidemiological studies in which the incidence of cancer in populations is found to vary (spatially or temporally) with exposure to the agent; and (3) analytical epidemiological studies (e.g., case-control or cohort studies) in which individual exposure to the agent is found to be associated with an increased risk of cancer." (Ibid, p. 18)

Nevertheless, OSHA notes that IARC considers that case reports and descriptive epidemiologic studies may provide at least "suggestive evidence".

The NCAB Subcommittee on Environmental Carcinogenesis summarized the types of evidence that suggest a positive association:

"Types of evidence suggesting that an agent is carcinogenic in humans include: neoplastic response directly related to exposure (both duration and dose); incidence and mortality differences related to occupational exposure; incidence and mortality differences between geographic regions related to different exposure rather than genetic differences and/or altered incidence in migrant populations; time trends in incidence or mortality related to either the introduction or removal of a specific agent from the environment; case-control studies; and the results of retrospective-prospective and prospective studies of the consequences of human exposures. Clinical case reports may also provide early warning of a potential carcinogen." (NCAB Report, 1977, p. 462; Exhibit B to Weinstein Statement)

The Temporary Committee for the Review of Data on Carcinogenicity of Cyclamate set the following criteria for judging epidemiologic data:

"The carcinogenicity of cyclamate in humans must be established on adequate evidence that exposure to it alone, or in combination with one or more other chemicals, increases the risk of malignant neoplasms in humans to levels higher than in a comparable cohort not exposed (or exposed at a lower dose) to cyclamate.

"Some of the acceptable evidence includes: response directly related to exposure (both duration and dose); incidence and mortality differences between countries or other geographic areas; altered incidence in migrant populations; time trends in incidence (including lowering incidence when specific agents are removed from the environment); and prospective studies of the consequences of exposure. The absence of such evidence, however, does not establish the safety of cyclamate due to the insensitivity inherent in population-based epidemiologic studies." (Temporary Committee for the Review of Data on Carcinogenicity of Cyclamate, 1976, p. 3; Appendix 2 to Griesemer Statement)

From these quotations one can see that the crucial point is the establishment of the causal link between exposure and effect, revealed in higher incidence of cancer as compared to those not exposed. However, none of these expert committees specified any rigid criteria for the evaluation of evidence.

Both E.I. DuPont De Nemours and Company and AIHC submitted the same proposed criteria for evaluation of positive epidemiological data:

"*Criteria.*" A substance shall be classified as a known human carcinogen on the basis of valid epidemiological data or other valid human data. Such data should be evaluated in light of:

"1. The magnitude of the association between exposure and excessive age-standardized risk (as measured by relative risk analysis or Standard Mortality Rate) and the statistical confidence limits.

"2. The size of a study population and the number of cases of cancer.

"3. The specificity of the type and site of cancer.

"4. Confirmation, or lack of confirmation, by other independent studies.

"5. The suitability of the control group used for the confirmation of excessive risk, particularly the extent to which exposed and control groups are similar in respects other than exposure to the suspect agent, e.g., ethnic, socio-economic, dietary, exposure to other chemicals, use of tobacco.

"6. Whether there is evidence of a dose-response relationship.

"7. Whether the observed carcinogenic effect is likely to be direct or indirect, e.g., explicable in terms of a biological mechanism which is irrelevant to the occupational exposure.

"8. Whether well-documented individual case reports or studies show that the substance in question has in fact, or with a high degree of probability, caused cancer in humans, even though the number of cases is too small to apply epidemiologic or statistical tests." (AIHC Alternative Proposal, pp. 61–62; DuPont Recommended Alternative (Appendix A), pp. 45–47)

Dr. J. V. LeBlanc (Phillips Petroleum) proposed the following criteria:

"Category I human epidemiologic evaluations should include as a minimum either a single prospective study including medical histories, air monitoring data for the specific chemical substances in question, lifestyle information, such as smoking, alcohol consumption, and dietary information, or two retrospective evaluations with two of the following items different in each study: (a) the time interval of exposure, (b) the principal investigator, or (c) the plant or industrial site evaluated. Retrospective studies should include detailed medical histories and air monitoring data for the specific chemical substance in question. A ten year work history is necessary for all epidemiologic studies." (LeBlanc, S. 4–5)

Dr. Robert Snyder cited (S. 14) A. B. Hill's "Rules of Evidence of Cause and Effect Relationship" as a guideline for evaluating positive epidemiologic data:

"1. Strength of association.

"2. Consistency (reproducibility in time and space).

"3. Specificity (uniqueness in quality or quantity).

"4. Temporality (congruous sequence in time).

"5. Biological gradient (proportionality between exposure and outcome).

"6. Plausibility (biological possibility).

"7. Coherence (biological compatibility).

"8. Experimental verification (biological modeling).

"9. Analogy (biological extrapolation)."

(Hill, 1965: for full discussion see Lilienfeld *et al.*, 1967, pp. 91–99)

Hooker Chemical Co. proposed an elaborate scoring system to express in numerical form the adequacy of epidemiologic studies and the applicability of these results. The factors to be considered were listed in an "Evaluation Checklist":

"1. Specificity of site.
"2. Effect direct or indirect.
"3. Suitability of control group.
"4. Size of study population.
"5. Sensitivity of study.
"6. Potency." (Hooker, S. 35)

API proposed the following set of criteria as part of a "minimum" number of steps to be followed in evaluating epidemiologic studies:

"D. Determinations of carcinogenicity should be based on appropriate weighting and consideration of all pertinent scientific studies including negative as well as positive studies. Given the present state of knowledge, we believe the following steps should be considered at a minimum:

"1. Sound epidemiological studies, whether negative or positive should be accorded the appropriate weight in identifying confirmed human carcinogens. The following criteria should be used in evaluating human data on carcinogenicity:

"a. The specificity of the type and site of cancer.

"b. The size of the study population and the number of cases of cancer.

"c. The statistical validity of the exposed population size.

"d. The suitability of the control group used for the confirmation of excessive risk, particularly the extent to which exposed and to which control groups are similar, in respects other than exposure to the suspect agent—e.g., ethnic, socio-economic, dietary, exposure to other chemicals, use of tobacco.

"e. The magnitude of the association between the number of persons exposed and the excessive number of cases of cancer when compared to a group at standardized risk and the statistical confidence limits of association.

"f. Whether well-documented case reports or studies show that the substance in question has with a high degree of probability, caused cancer in humans, even though the number of cases is too small to apply epidemiologic or statistical tests.

"g. Confirmation, or lack of confirmation, by other independent studies.

"h. The possible role of host factors such as congenital and genetic diseases, immune deficiency diseases, acquired diseases and multiple primary neoplasms.

"i. The possible contribution of other environmental factors such as tobacco, alcohol, radiation, drugs, diet, air and water pollution, and viruses and other microbes.

"j. Whether there is evidence of a dose-response relationship.

"k. Whether the observed carcinogenic effect is likely to be direct or indirect—i.e.,

explicable in terms of a biological mechanism which is irrelevant to exposure to the suspect substance." (API, 1978, pp. A3–A4; Hearing Exhibit 77)

In contrast to this, one of API's own exhibits emphasized strongly that the evaluation of positive studies is primarily a matter of judgment rather than rigid use of specific criteria:

"The conduct of each epidemiologic study requires some judgment about whether an association is of causal significance. The Surgeon General's report on Smoking and Health concludes an introductory discussion of judgment and causal inference with the following:

" 'The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability.'

"The criteria most appropriate for evaluating an association are consistency, strength, temporal relationship, coherence and specificity. The criterion of consistency is analogous to experimental replication, but may also rest on the demonstration that diverse investigative approaches produce similar results. The strength of an association may be expressed in terms of relative risk ('risk ratio', 'odds ratio') and population attributable risk ('etiologic fraction'). Coherence embraces the criterion of biologic plausibility, although it should not discourage the consideration of unorthodox, innovative hypotheses. The temporal criterion requires that the presumed cause must always precede the observed effect, whereas the criterion of specificity implies that there is a predictive pattern of effect(s) likely to occur with frequency greater than random chance if the antecedent event or complex of events were of causal significance." (Schottenfeld *et al.*, 1978, pp. 5–6; Hearing Exhibit 219)

AIHC proposed lengthy guidelines for evaluation and use of occupational epidemiologic cancer studies.

"The following guidelines are intended to describe major factors in assessing the strengths and limitations of epidemiologic studies, the use of which in turn will assure maximum and appropriate utilization of valid human data. The guidelines are not intended as a check list for accepting or rejecting a study. All data on human exposure to a substance should be considered in attempting to reach a judgment on the human health risks from occupational exposure. Although studies that satisfy all of these guidelines should receive greatest attention, studies that do not should receive attention commensurate with their strengths and weaknesses. There is no substitute for the evaluation of individual studies by highly qualified experts, such as the Data Evaluation and Classification Panel recommended in the AIHC Alternative." (AIHC Post-hearing Brief, App. D, p. 1; Hearing Exhibit 251)

AIHC proceeded to list and discuss a number of features of an epidemiologic study which should be taken into account:

"I. Description of Study Features
A. Population Characteristics
1. Study Population
2. Comparison Population
3. Sampling Procedure and Sample Size
4. Observation Period
B. Exposure Characteristics
1. Occupational Exposure Under Study
2. Confounding Variables
C. Health Effect
D. Procedures
E. Case Presentations
II. Analytic Method
A. Data Presentation
B. Data Analysis
III. Evaluation & Results and Their Interpretation
A. Hypothesis Testing
B. Limitations
C. Bias
D. Power"
(AIHC Post-hearing Brief, pp. D1–D10, headings only)

AIHC then gave the following general criteria for accepting a positive result:

"A study is classically considered to be 'positive' (show an effect) when the upper confidence limit of the frequency in the comparison population falls below the lower confidence limit of the frequency in the study population and this difference is not explained by the study's limitations, biases, or confounding variables." (*ibid.*, p. D10)

OSHA recognizes that many factors complicate the conduct and evaluation of epidemiologic studies, and that "false positive" results may sometimes be obtained in poorly designed or poorly conducted studies. However, on review of the evidence in the Record, OSHA concludes that it would be unjustified and inappropriate to adopt any rigid set of criteria for the acceptance of positive epidemiologic studies. As the above discussion indicates, the major participants in this proceeding, although listing many "criteria" for the evaluation of studies, in fact recommended the use of expert judgment in interpreting these criteria, rather than any rigid sets of rules. The factors which are common to the above lists of criteria are in fact factors of well-known importance in epidemiology, which would be taken into account by any competent scientist or group of experts evaluating a study. On the other hand, some of the factors included in the above lists could not be adopted as required criteria because they would result in improper and unjustifiable delays in acceptance of clearly positive results. For example, Phillips Petroleum's proposed requirement for either a 10-year prospective study or two 10-year retrospective studies would result in unreasonable delays in regulation of chemicals for which good positive data exist. In fact, some of the long lists of criteria and factors to be considered in evaluating studies that were presented in the Record would serve little purpose except to delay or prevent the acceptance of studies that would meet the general standards of informed professional epidemiologists. OSHA notes in particular that a widely quoted textbook gives a much less restrictive criterion for acceptance of causative relationships:

"We therefore recognize that a causal relationship exists whenever there is evidence that possible etiological factors form part of the complex of circumstances which increases the probability of developing a cancer, and that in its diminution or absence the frequency of the cancer is diminished (Lilienfeld et al., 1967, p. 87)."

The key to the reasonable interpretation of positive epidemiologic studies, as AIHC and others pointed out, is thus the exercise of good scientific judgment. This concept is inherent in OSHA's use of the word "causes" in its definition of "potential occupational carcinogen" (see Saffiotti, S. 6–8). Thus OSHA intends to apply good scientific judgment in the interpretation of epidemiologic data. OSHA will consider the factors as those enunciated by Lilienfeld *et al.*, IARC and AIHC, rather than follow, by rote, any rigid set of rules, in the evaluation of the data for any given substances. To do otherwise would be to reject the arguments of all parties that OSHA should exercise scientific judgment in the determination of whether the data are or are not sufficient. OSHA is aware of its responsibility to "assure the safety and health of American workers", and repeats its intention to take regulatory action whenever there is reasonable evidence that a risk exists:

"The basis for these criteria initiating a Category I classification are predicated upon the discussions above and here. First, despite the inherent limitations of epidemiological studies in humans, where such studies indicate positive results, even where there is a small cohort of workers, OSHA believes that exposure to such a substance gives rise to great concern. Thus, the proposed set of regulations provides that such evidence in humans at least presumptively initiates a Category I classification, unless the evidence is "only suggestive" in which case the evidence initiates the Category II classification. It is only where the human evidence is "totally inadequate" that OSHA will classify the toxic substance as a Category III Toxic Substance."

OSHA believes that responsible public regulation in matters concerning human health requires no less action or caution. (42 FR 54170)

6. Alleged "Non-Positive" Studies and Criteria for Their Acceptance

a. General arguments for the validity of "non-positive" studies.

Perhaps the most vigorously debated issue relating to human studies was whether OSHA was correct in proposing that "in general", positive animal data should supersede "non-positive" human data. Many participants claimed that this position was scientifically unsound and that in fact, for a number of substances, "non-positive" epidemiological studies existed and should be given greater weight than positive animal studies. In addition to the general objections quoted above from AIHC, Reserve Mining, AISI, and Dr. Clemmesen, several parties addressed specifically the validity of "non-positive" data. For example, Ethyl Corporation, citing Dr. Irving Kessler (John Hopkins Univ.), argued as follows:

"In its categorization scheme for carcinogens, OSHA proposes to use only positive human epidemiological data. Although OSHA is correct that a number of factors can limit the significance of negative human epidemiological studies, none of these factors justify [*sic*] disregarding such studies entirely. As Dr. Kessler notes, the "notion that negative findings in epidemiological studies are to be ignored as worthless is not only unscientific and illogical but counterproductive in the search for reasonable methods to protect man from environmental hazards." (Kessler, S. 6) "For, if substantial and consistant negative findings are to be ignored, by what logic then should substantial and significant positive findings be accepted?" (Ethyl Corp. Post-hearing Brief, p. 63; Hearing Exhibit 232)

Dr. Alonzo Lawrence (Koppers) stated that:

"It would appear that OSHA's principal concern in the future will focus on the health effects of existing chemicals. In such matters, it would appear that human epidemiological evidence, particularly negative findings with regard to cancer induction, should be regarded as valuable information and considered more fully in the regulatory process.

"In fact, the requirement for industrial hygiene monitoring and medical examinations in all existing and proposed occupational health standards are de facto recognition of the importance of prospective epidemiological information in the practice of occupational health and regulatory activities." (Tr. 7778)

Dr. Carl Dernahl (Union Carbide) stated:

"If four or five or ten cancers in 100 animals can result in a judgment that a material is a carcinogen, what justification is there for refusing to accept human data covering a span of several decades and involving several hundred to perhaps a few thousand people when data shows no carcinogenic relationship?". . .

"In the last analysis, valid epidemiologic observations related to experience of people should be given primary evidentiary weight in making judgments of potential harm to people, rather than complete reliance on rats, mice or a strain of bacteria." (Tr. 6597–6598)

Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska) offered the following comments on OSHA's preamble discussion of Human Studies:

"This section is devoted, with reason, to the complexities of the epidemiological method. However, it is again too extreme and totally rules out the use of negative epidemiological intelligence under any circumstances. This is counter to common sense and to recently expressed scientific viewpoints." (Shubik, S. 12)

Pittsburgh Plate Glass commented as follows:

"Epidemiological evidence has been the primary basis for issuance of standards for suspect human carcinogens. This should remain unchanged. . . . Much valuable information can be obtained from properly conducted epidemiological studies. If epidemiological studies are used to identify potential risk or cancer association, then they should also form the basis as evidence of minimal or no risk of cancer from the actual exposures that occurred in workplace environment." (PPG, S. 14)

The Soap and Detergent Association also objected to OSHA's proposal that positive animal data should supersede "non-positive" data:

"We believe that the weight to be assigned to epidemiological data should be placed in proper perspective. Where sufficient epidemiological data is available it should be given greatest weight in characterizing risk. Thus, even where appropriate animal data documents potential risk, epidemiological data should be given great weight in the *choice* of any regulatory response." (SDA, S. 6, emphasis in original).

Drs. Robert Snyder and Anthony Triolo (AISI) made the following statement:

"Perhaps the more significant failing of the OSHA proposal is the outright refusal to recognize that negative results in a human epidemiological study should, at least in some cases, outweigh a demonstration of carcinogenicity in animals. Thus, negative human data should outweigh positive (though weak or limited) animal results if the epidemiological study was carefully structured, based on data that is known with a high degree of confidence and shows results that unambiguously demonstrate the absence of cancer induction. Where the negative human data is the result of a less optimal study, it need not necessarily outweigh positive animal data. Admittedly, there may be few instances in which convincing negative human epidemiological results will exist for a substance that has produced positive results in animals. Nevertheless, the fact remains that human data is clearly the most relevant data in assessing the cancer risk in humans, and it cannot be emphasized too strongly that a thorough evaluation of any human epidemiological data is an absolute requirement regardless of how persuasive the animal data appears to be." (Snyder and Triolo, S. 14–15, footnote omitted)

Reserve Mining Co., like other participants, argued that the fact that epidemiologic studies can give reliable positive results means that weight should be placed on negative results:

"The value and validity of human epidemiological evidence cannot be as easily cast aside as OSHA appears to prefer. Indeed, while citing and quoting the views of Cole and Goldman (42 FR 54155), OSHA overlooks the significance of what these authors state:

"Existing epidemiological methods are adequate for demonstrating carcinogenic hazards in the work environment even when the excess risk is rather small and the disease in question is relatively common in the general population. However, this capacity for recognition depends on the actual occurrence of disease and, by itself, has [no] preventive or control value. Ideally, we should prevent occupational cancers from occurring; failing that, we should strive to eliminate [a] fatal outcome in cases that do occur. Technical and epidemiologic approaches are likely to be useful both in the area of prevention and mortality reduction." (Cole and Goldman, in Fraumeni, Persons at High Risk of Cancer, National Cancer Institute, 1975, at p. 177, emphasis supplied)." (Reserve Mining, S. 14)

b. Nature and limitations of "non-positive" studies

The above comments, and others in the Record, reflect a fairly widely-held opinion that some weight should be placed on "non-positive" results of epidemiological studies. However, as shown in detail below, other witnesses argued strongly that "negative" or "non-positive" results have many uncertainties and cannot be given any weight. In view of the importance of this issue, OSHA has reviewed and analyzed the Record carefully and in detail in this and the following section of the preamble. Initially, OSHA draws attention to three major deficiencies in the testimony presented in support of

the use of negative epidemiologic studies.

1. Very few of the participants made any note of or distinction between the qualitative and quantitative use and interpretations of "negative" or "non-positive" studies. In principle, it is impossible to prove a negative with any study of a finite size. An epidemiologic study, like any other screening test, is an instrument of limited sensitivity. Thus, however well a study may be carried out, the most that can be concluded reliably is that it failed to show an effect within the limit of sensitivity imposed by the study design. This point was concisely expressed in the report of the NCAB Subcommittee on Environmental Carcinogenesis:

"Negative epidemiological data may not establish the safety of suspect materials. Negative data on a given agent obtained from extensive epidemiological studies of sufficient duration are useful for indicating upper limits for the rate at which a specific type of exposure to that agent could affect the incidence and/or mortality of specific human cancer" (NCAB Report, 1977, p. 462).

However, most of the witnesses who quoted this paragraph in support of the use of "negative" epidemiologic data failed to make this fundamental distinction between the qualitative identification of a hazard to humans and the quantitative assessment of the risk. Indeed, after careful review of the comments on this issue, OSHA has found only a handful of comments which specifically proposed the use of "negative" epidemiologic data "for indicating upper limits for the rate at which a specific type of exposure to that agent could affect the incidence and/or mortality of specific human cancers." These specific proposals, which have a substantial conceptual and theoretical basis, will be discussed in the next section (B.7 below). Here we review the less specific arguments that "non-positive" human studies should offset, outweigh or supersede positive results in animal tests insofar as the qualitative identification of a carcinogen is concerned. We note at the outset the opinion of the NCAB Subcommittee that "Negative epidemiological data may not establish the safety of suspect materials."

2. A second deficiency is that few witnesses recognized that reliable results showing no risk are *inherently* more difficult to establish than positive results in epidemiology. As pointed out in Section 4 above, the presence of small confounding factors is of little consequence when a large excess risk is observed, but may be of major consequence if the study reveals only a small excess risk, or no excess risk at all (see the report of the NAS Committee for a study of Saccharin and Food Safety Policy, quoted above). For example, if a ten-fold excess cancer frequency is observed, a minor source of bias or confounding factor is of much less consequence than if the cancer frequency is only 1.5 times that in the control group. The same comments apply to sample size: a large excess risk can be identified in a small group of workers, whereas many thousands of workers must be studied to establish that relative risks are less than 2.0.

3. A third point is that many witnesses argued for the use of negative epidemiologic data as though they were to be considered in isolation. In fact, under this regulation, substances will be considered for regulation as Category I potential carcinogens only when there is evidence that is more than suggestive of their carcinogenic activity, either in animals or in humans. Thus, the issue is not whether non-positive epidemiologic data should be given weight, but whether such data should be given *sufficient weight to outweigh positive evidence, which often may be very strong indeed.*

In addition, most of the participants failed to recognize the severe limitations of "non-positive" epidemiologic data. Even the definition of a "negative" epidemiologic study proved difficult: those who attempted to define a "negative" study merely defined it as a non-positive study:

"A negative epidemiologic study would be one that fails to find an association between, say, the variable under consideration, that is, the exposure to a substance, and subsequent development of disease or excess mortality . . . Or you could say fails to find the association between independent and dependent variables, if you want to be more generic." (Morgan, AIHC, Tr. 3673)

Dr. Mitchell Zavon (NACA) stated:

"I would define negative epidemiological data simply as a properly done epidemiological study which did not come up with evidence of associative relationship between an exposure to a substance and some aberrant physiologic response, whether this be development of malignancy or more commonly, other effects." (Zavon, Tr. 5416)

However, this term is not one that is usually used in the field, as Dr. Zavon pointed out:

". . . I would simply say that at the limit of our measurements, we were unable to detect any effect, and that I would call, if you wished, a negative epidemiological study. I would not ordinarily use that term. I would simply say that the epidemiologic study did not indicate any positive correlation." (Zavon, Tr. 5417)

In addition to the general comments quoted in the previous section about the insensitivity of epidemiologic studies and the difficulty of conducting them in an unbiased way, a large number of comments were made about the specific limitations of "negative" studies.

Dr. David Rall (Director, NIEHS) and Dr. Marvin Schneiderman (NCI) introduced the report of the National Academy of Sciences' Safe Drinking Water Committee, whose conclusions on the value of epidemiologic studies relative to that of animal carcinogenicity studies were as follows:

"Studies in laboratory animals must be used to predict the safety of environmental chemicals. Human epidemiological studies cannot be used to predict nor assure safety, for several reasons:

"1. Epidemiology cannot tell what effects a material will have until after humans have been exposed. One must not conduct what might be hazardous experiments on man.

"2. If exposure has been ubiquitous, it may be impossible to assess the effects of a material, because there is no unexposed control group. Statistics of morbidity obtained before use of a new material can sometimes be useful, but when latent periods are variable and times of introduction and removal of materials overlap, historical data on chronic effects are usually unsatisfactory.

"3. It is usually difficult to determine doses in human exposures.

"4. Usually, it is hard to identify small changes in common effects, which may nonetheless be important if the population is large.

"5. Interactions in a "nature-designed" experiment usually cannot be controlled." (NAS, 1977a, p. 28; Appendix I to Rall Statement)

In the report *Cancer Testing Technology and Saccharin,* the Advisory Panel reviewing the negative epidemiologic data made the following comments:

". . . negative epidemiological studies are far more difficult to interpret. Humans are usually exposed to carcinogens in doses far smaller than are used in animal experiments. The effects are consequently less frequent, and the number of people whose experience needs to be judged to detect the cancer effect is much greater.

"Lack of certainty as to the validity of the data on exposure in case-control studies is a further reason for reservations in interpreting negative findings. Only a portion of the population uses saccharin, and the use of statistics from the total population may dilute any association that exists among the users—perhaps to the point of making it unobservable." (OTA, 1977, p. 27, Exhibit C to Weinstein Statement)

In a paper presented to the New York Academy of Sciences, Drs. Schneiderman, DeCoufle, and Brown of NCI presented the following criticisms of some so-called "negative" occupational epidemiologic studies:

"However because of limitations in study design (including documentation of true

exposure), analysis, and interpretation of results, we believe these studies do not conclusively demonstrate that these materials are 'safe' even within the particular group under study.

"The deficiencies inherent in these studies can be classified broadly into two categories. One is the inappropriateness or inadequacy of the study group, i.e.,

"1. the exposure was not really present in the environment or, if it was, there was no uptake by the 'exposed' persons (e.g., non-respirable sized material);

"2. the exposure was of such short duration because of high turnover rates in the industry or was at such a low level that, coupled with a small study group, demonstration of an effect, i.e., a signal above the background noise, would be very difficult

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"The second set of problems is more statistical. Specific troubles include:

"1. Invalid population-at-risk. For example, looking only at currently employed workers, as in the DuPont study of cancer incidence. Cancer incidence and mortality appeared low because the study was cross-sectional rather than longitudinal, i.e., it was a 'snapshot' rather than a cumulative observation of a fixed population over time.

"2. Incomplete enumeration of health outcomes (e.g., deaths) in the study group.

"3. Incorrect cause-of-death classification (e.g., Pinto's smelter workers, some of whose deaths were charged to pneumonia (the immediate cause) rather than the lung cancer which led to the pneumonia).

"4. Inappropriate comparison group (e.g., comparing one high risk group to another high risk group or comparing a low-dose sub-cohort to the entire cohort in which high doses are dominant).

"5. Starting with a study group whose average age at entry to study is very young and, when coupled with the length of follow-up, results in an inadequate number of person years at older ages where chronic diseases are most prevalent.

"6. Inadequate number of person-years at risk of dying.

"7. Latency phenomenon not considered either in determining the length of the follow-up period or, if follow-up interval was adequate, analysis did not subdivide risk estimator by latency intervals (e.g. over entire period of observation there may be little or no effect observed when all latency intervals are combined but when split into sub-intervals, an elevated risk ratio may appear only after 20 or 30 years since first exposure).

"A general problem that exists for epidemiological studies attempting to relate exposure to a material (dose) and health outcome characterized by a long period of clinical latency (effect) is the measure of dose. Problems with dose estimation arise in several ways.

"1. Estimation of the levels to which individual study group members were exposed in the past often involves making 'guesstimates' about historical conditions. One wonders how realistic it is to build dose-response curves from the past for determining thresholds when currently there are serious problems about how to measure levels of various contaminants. It is possible to have such a wide choice in making dose estimates for human populations that contradictory conclusions can be reached from independent epidemiologic studies for the same populations.

"2. The model of how the disease comes about, which we need when relating dose to response, especially when the dose is changing during the followup period is not obvious." (Schneiderman *et al.*, 1978, pp. 19–21; Appendix D to Schneiderman Post-hearing Comments)

API presented a paper which, while claiming that epidemiologic studies may identify the "absence of risk", recognized that such studies have limitations:

"Properly designed epidemiological studies may serve to identify the absence of risk. The validity of any inference about minimal or no risk may be determined by the adequacy of exposure and follow-up information. The ability to detect significant differences in risk will depend in part upon a statistically adequate sample that will enable the determination of differences in risk if they do indeed exist. However, a limitation of the epidemiologic method may be its insensitivity to measure, in retrospect, single or complex low-level chemical exposures that give rise to small increases in risk. In addition, because of the long latency period, the orientation is post-hoc and not predictive or applicable to those chemicals that are now being introduced." (Schottenfeld et al., 1978, p. 7; Hearing Exhibit 219)

This passage unequivocally claims that negative studies "may serve to identify the absence of risk." However, other witnesses pointed out that the insensitivity of epidemiologic studies imposes an upper limit on the magnitude of effects that can be detected. As Dr. Richard Bates (NIEHS; FDA) stated:

"Few epidemiological studies of occupational cancer have been of adequate sensitivity to detect anything smaller than a 50% increase in the incidence of cancer over that found in the general population. Weakly carcinogenic agents, that is those capable of inducing cancer only if the most highly susceptible individuals at the level to which the worker population is exposed, would not be detected by most studies." (Bates, S. 7)

His opinion was shared by many other witnesses:

"Well, I think I referred to the tremendous difficulty of obtaining such negative data. Firstly, we do not have the population large enough to achieve negative data that would have a statistical power that would be useful in human circumstances. We can only say that something is perhaps not producing five times as much of this cancer as one might expect, and negative data of that order is not really adequate to protect workers." (Nicholson, Tr. 1756)

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"Well, they are insensitive. I do not think—it is not worthless to do epidemiological studies. I think they are very worthwhile to do for a variety of reasons, and I think we ought to put more effort into this, but negative data in such an insensitive test frankly is not worth very much for making a decision, a regulatory decision." (Harris, Tr. 2017)

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"... human epidemiology studies are very limited in sensitivity, that the only thing one can hope to detect using that method are very potent carcinogens.

"I mean, that tends to be generally true, is that you can only detect high incidence of cancer, and that is of course, because of the background rate that we all have to deal with, the 25 percent incidence already in people." (McCann, Tr. 1588)

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"In the weak carcinogen area you can demonstrate perhaps animal positive results and probably cannot demonstrate comparable human results." (Lawrence, Tr. 7785)

Dr. Irving Kessler (Johns Hopkins Univ.) agreed that epidemiologic studies are insensitive, but did not consider that the small risks that could not be detected would be of concern:

"One of the weaknesses of epidemiological studies is—human epidemiological studies, noted—is that they cannot dectect low level risks. I think technically—and I will use that word a lot during my presentation—technically, that is correct. Epidemiological studies of the kind, of the magnitude normally done on hundreds or a few thousand patients cannot detect increased risks at the level of one percent or one-tenth of a percent or a hundredth of a percent; however, it is my contention that such risks, given the enormous variability that exists among people anyway, and in the conditions of any study done under any circumstances, given this enormous built-in variability, what does a risk of one percent, a tenth of a percent or a hundredth of a percent mean?

"To me it means an abstraction; a statistical abstraction having no biological reality whatsoever." (Kessler, Tr. 6875)

Further discussion of the problem of quantitative estimation of the upper limits on risk consistent with the results of "non-positive" studies is given in the next section.

Dr. Irving Selikoff (Mount Sinai School of Medicine) gave an extremely important and informative example of the insensitivity of the epidemiologic method:

"I think that Dr. Nicholson's mention before of the asbestos related cancer of the lung in non-smoking asbestos workers teaches us a great deal. We looked at a fairly good-sized group in New York City of the 370 men. These were all more than 20 years from onset because they were the survivors of the original 1943 cohort, and yet, by 1967 we did not see a single case of lung cancer among the non-smokers. Now, if asbestos did not cause mesothelioma and if there were no cigarette smoking among us, I would not be able to tell you if asbestos is a carcinogen or not. It was not until we followed 2000 people

for 10 (more) years that we were able to find eight cases against 1.82 expected. It took a great deal of work to get this basic epidemiological data, and if studies are not done with that duration and at that size, then all you can say is you did not look. And unfortunately, we do not often have the opportunity of looking. And there are many reasons for this but that is another question." (Selikoff, Tr. 1757)

Another aspect of the insensitivity of the epidemiologic method is the long latency period between exposure and effects; failure to follow-up on study groups for sufficiently long time periods would lead to a "false negative" result. Mr. Richard Peto (Oxford University) commented on this point:

". . . if in theory you have observed 50,000 people for a period of about 40 years, and you can distinguish well between those who are exposed and those who are not exposed, then you can start making statements. And particularly the problems arise because counts of risks for quite important carcinogens may be negligible for even decades of continued exposure. It may be that 40 years continued exposure is extremely dangerous, but that 15 years of continued exposure confers what is a negligible risk until further time has elapsed." (Peto, Tr. 2542) (see also Drinking Water and Health, NAS, 1977a, p. 51)

As Mr. Peto (S. 28–31) and Dr. Matthew Meselson (Harvard Univ.) pointed out, one cannot expect that the high dosed workers would necessarily show a reduced latency period:

"So I believe that there is no basis whatever for assuming that the age distribution would be changed by the dose. So that if you give a little bit of a carcinogen and you find that the age distribution is a certain one—let's say that half of the tumors are in people 50 and lower and whatever—that if you give more of the carcinogen it will still be true that half of the induced tumors are in people in that age group and lower, that age distribution will not change unless, of course, you give so much that you begin wiping out the oldsters so there are no oldsters to contribute to that category.

"Anyway, that is what we have to assume, I believe. I think there is pretty widespread agreement that that is what we have to assume; that the time dependence follows that Weibull equation, and if you assume that then the problem with human epidemiologic studies of short duration is that they are so exceedingly insensitive because of that factor." (Meselson, Tr. 1535–1536)

The long latency period also results in difficulties in defining the nature of the exposure:

"Two more difficulties affect virtually all studies of occupational carcinogenesis. Most cancers probably have an "incubation" period of 20 years or more. In industrialized countries, technologic advances and changing needs are such that many industries evolve rapidly. As they do, new jobs and exposures come into being and others cease to exist. Thus, a given study might uncover a carcinogenic exposure that has already ceased. At the same time, the more recent replacement exposure cannot be evaluated because the requisite incubation period has not elapsed." (Cole and Goldman 1975; p. 169; Exhibit to Squire Statement)

However, even if these problems with latency and duration of exposure are resolved, Dr. Umberto Saffiotti (NCI) pointed out that due to the uniqueness of exposure situations, it would be impossible to extrapolate safety for all workers exposed to a substance from a single negative study:

"In discussing human studies it is important to stress that occupational epidemiology seldom provides results of sufficient extent and accuracy to guarantee adequate negative evidence and to establish that the usage of a substance is safe in the face of positive experimental findings. Interindividual variability, previous or concurrent histories of other occupational or environmental exposures, special conditions of exposures (e.g., during pregnancy) may interfere in the extrapolation of such apparently negative observations from one occupational group to another."(Saffiotti, S. 29)

Dr. Richard Bates (NIEHS; FDA) concurred:

"So the best that we can say with a "negative" human epidemiologic study is under the conditions of exposure of this particular group of people—that is, whatever level of exposure they have had for whatever period of time they have had—this number of people did not have an increase in cancer incidence great enough to be statistically identified." (Bates, Tr. 623)

Another factor which affects the sensitivity of an epidemiologic study is the size of the study group. According to Dr. William Nicholson (Mount Sinai School of Medicine):

"We do not have the population large enough to achieve negative data that would have a statistical power that would be useful in human circumstances. We can only say that something is perhaps not producing five times as much of this cancer as one might expect, and negative data of that order is not really adequate to protect workers. I think the prudent course is to go with the animal data in the absence of what would be substantive negative data." (Nicholson Tr. 1756)

Many negative studies are suspect because not all sites of possible cancer induction have been analyzed, as Dr. John Berg (Colorado Regional Cancer Center) demonstrated in his discussion on Saccharin:

"What is fallacious about much of the discussion about saccharin is that its safety is said to be proven if it can be demonstrated that there is no excess risk of *bladder* cancer. Most chemical carcinogens show target organ specificity and produce cancer in only one or two tissues when fed or injected into a particular animal strain. This is because most chemicals have to be activated and changed to an ultimate carcinogen before they are dangerous. Different compounds require different sets of enzymes for activation. These enzyme sets exist in different tissues. Their location in the animal varies from species to species . . . A study is not negative unless *all* cancer risks are shown to be low enough to be acceptable." (Berg, S. 23–24).

The unpredictability of the organ specificity of a carcinogen in humans was demonstrated by the work of Hammond and Selikoff on asbestos workers:

"We also looked at all other sites. Dr. Hammond analyzed expected and observed rates for all sites of cancer, indeed, for all diseases. We found a significant excess, statistically significant, for cancer of the larynx, cancer of oral pharynx and cancer of the kidney, with roughtly two to three times as many as expected.

"However, even knowing and having proven in human circumstances that this agent was a human carcinogen, we found that this did not hold for a number of other sites. In other words, we could not predict even based on human experience, that something was going to be a carcinogen for this or that other tissue.

"At post-mortem, for example, asbestos workers tend to have much asbestos, many fibers, in the liver. They get there through the bloodstream. Yet, there was no excess of liver cancer. We found an excess of cancer of the kidney; we did not find an excess of cancer of the bladder, where there were nine or ten expected, and only eight observed. There was no excess of leukemia and lymphoma, there was no excess of cancer of the skin, pancreas, et cetera. In other words you just simply were unable to predict, not merely from animal experiments, but even from human information, you could not predict entirely in this regard." (Selikoff, Tr. 1695–1696)

Problems like those listed above have led some scientists, like Mr. Peto (Peto, Tr. 2542) or Dr. Renate Kimbrough (CDC) (Tr. 1776–1777) to state that they have never encountered a good non-positive epidemiologic study, in the sense that it would demonstrate the safety of a substance (See also Drs. Upton (Upton, Tr. 318) and Yodaiken (Yodaiken, Tr. 2943)). Dr. Kessler (Johns Hopkins Univ.) suggested that these weaknesses are simply an invitation for the conduct of better epidemiologic studies (Kessler, Tr. 6877). Although better epidemiologic studies are indeed needed, the issue before OSHA in this proceeding is the protection of workers today, not the identification of carcinogens by the use of human data tomorrow. The evidence quoted above indicates that epidemiologic studies can only detect effects within the limits of sensitivity of the experimental design. Most studies have been of insufficient

sensitivity to provide convincing evidence that carcinogenic risk is substantially lower than that indicated by presumptive positive evidence derived from other sources. At the least, "non-positive" studies would have to meet extremely strict standards before weight could be placed on them in opposition to positive evidence in humans or experimental animals. Because of the possibility that such strict standards however may be met and the need for scientific flexibility, OSHA has provided for consideration of such studies in the qualitative determination of a hazard, if strict threshold standards of proof are met, as discussed below.

c. Criteria for Evaluation of "Non-positive" Epidemiologic Studies

Several witnesses were asked to suggest criteria for evaluating epidemiological evidence, especially so-called "non-positive" studies. Many witnesses emphasized the primary importance of exercising professional judgment, especially in the face of conflicting animal data. As Dr. Robert Olson (St. Louis Univ.) stated:

"What I am saying is that one has to start with animal experimentation, which may be a very important red flag about a given compound, would indicate its potential for carcinogenesis in a given species under given conditions and then go from there. But when one puts into juxtaposition a lot of negative clinical information and a few positive animal tests in one species—and that applies to saccharin, to TCE, to DDT—then one has a problem that requires judgment by experts and not rote procedures." (Olson, Tr. 3234)

In fact, Dr. John Thorpe (API) suggested that, rather than establish criteria at all, OSHA should rely on the judgment of "a competent epidemiologist" in conjunction with other scientists who would be able to determine the quality of any epidemiologic data submitted for purposes of regulation (Tr. 4582).

Dr. Robert Morgan (Univ. of Toronto) believed that the use of criteria and of scientific judgment should be applied after calculation of statistical significance is made:

"Let me say that I do not think it is the job of the epidemiologist to set an arbitrary figure at which you will believe there is an association or lack of an association. The job of the epidemiologist is to find out what the relative risk is, and give you some confidence limits. So I say that that kind of decision, then is not the epidemiologist's.

"A point that has not come out, really, is that there is no such thing as proof, and the acceptance or rejection of a hypothesis is really a subjective phenomenon based as much as possible on objective data, and that when we do statistical testing to test our hypothesis, supposedly, we are setting some arbitrary limits. And then we say if it comes in one way we will believe it; we may believe it if it comes in the other way . . ."

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"One of the criteria you have to build in as to whether to include the study in your weighting of positive and negative studies, is does the study make sense. There are far more problems in the design of the study and the data collection than there are in the statistical tests."

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". . . you can have some a priori criteria, but you will still, I suspect, reach a point where you must look at the study very carefully, and say what else other than those specified in the criteria might have gone on here?" (Morgan, Tr. 3678–3680)

One thing that makes the setting of criteria more difficult is that, as Mr. Richard Waxweiler (NIOSH) said:

"There is no one acceptable protocol that I know of for epidemiological studies." (Waxweiler, Tr. 2880)

The International Agency for Research on Cancer (IARC) proposed general guidelines for the evaluation of "negative" studies, while recognizing that such studies provide severely limited information:

"Analytical epidemiological studies that show no association between an agent and a cancer ('negative' studies) should be interpreted according to criteria analogous to those listed above: (1) There is no identifiable negative bias. (2) The possibility of negative confounding has been considered. (3) The possible effects of misclassification of exposure or outcome have been considered.

"In addition, it must be recognized that in any study there are confidence limits around the estimate of association or relative risk. In a study regarded as 'negative', the upper confidence limit may indicate a relative risk substantially greater than unity; in that case, the study excludes only relative risks that are above this upper limit. This usually means that a 'negative' study must be large to be convincing. Confidence in a 'negative' result is increased when several independent studies carried out under different circumstances are in agreement.

"Finally, a 'negative' study may be considered to be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elapsed since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years." (IARC, 1978, Vol. 17, pp. 19)

As discussed earlier, the NCAB Subcommittee on Environmental Carcinogenesis similarly specified that non-positive studies primarily serve to place upper limits on possible risks. The Subcommittee did not specify criteria for evaluation of such studies, except to emphasize that the studies should be "extensive" and "of sufficient duration." (NCAB Report, 1977, p. 462).

General considerations as to the development of standards for epidemiologic studies brought up the point that non-positive studies are more difficult to evaluate, and thus more stringent criteria should be laid down for non-positive than for positive studies:

". . . the advantage of a positive study is that you may be able to find an associated risk because of a high exposure level. But if you have a low exposure level, you may not be able to prove that there is not a risk. So that your epidemiology can operate positively with confidence at an earlier stage or with less available criteria, less of the criteria being met than would be the case for a negative study." (Wegman, Tr. 1682–1683)

Dr. Robert Hoover (NCI) voiced a feeling shared by several other scientists that non-positive studies are usually not even acceptable:

"I do not think you can ever apply a set of standards that would say a negative epidemiologic study or study that shows no risk supervenes a study which says that this agent is a carcinogen. And I referred to that in my testomony.

It is kind of a general principle of science that you cannot prove a negative. You can only fail to identify the positive, and usually a good, positive study supervenes a negative study.

Put on top of that the problem that epidemiology has of not really being able to go down to 10 percent excess risk, 5 percent excess risk. You can almost never, therefore, demonstrate something is not a carcinogen using epidemiologic methodology." (Hoover, Tr. 792)

Although there was general agreement that specific, rigid criteria could not be formulated, many witnesses offered suggestions as to factors important in the evaluation of non-positive epidemiologic studies.

The main points raised were these:

(1) The size of population sample under study is related to the sensitivity of the test, as a large study population is necessary to detect evidence of "weak" carcinogenicity (Olson, Tr. 3235–3236). Sufficient numbers are necessary to set fairly narrow confidence limits, which depend on what the background cancer rate is for the site under study (Berg, Tr. 1677–1678). Dr. David Rall (Director, NIEHS) suggested that a non-positive study would be more convincing if it were set up with sufficient numbers so that a 5 to 10% excess risk could be detected (Tr. 454). However, Dr. Robert Hoover (NCI) stated that:

". . . the lowest relative risk that I am aware of that is generally accepted by most epidemiologists as observable in an exposed group and attributable to that exposure is the

30 to 40 percent excess risk of childhood leukemia in kids who were exposed in utero in the last trimester, . . . so that is a relative risk of 1.3. So a relative risk of 1.04 is essentially non-detectable by an epidemiological study, at least non-detectable and attributable to causality". (Hoover, Tr. 789–790)

These comments were addressed fairly specifically to the quantitative problem of calculating upper limits on risk. By extension, these arguments indicate that only a study of infinite size could demonstrate that there is no risk whatsover. Indeed, Dr. Hoover pointed out that relative risks below 1.04 are not in practice detectable.

It is also essential to include in the study population a representative group of people, as one cannot extrapolate similar risks or lack thereof between sexes, races, etc. (Berg, Tr. 1678). And as several witnesses have agreed, appropriate control groups are necessary (similar to the study group in basic demographic characteristics and other factors such as smoking patterns).

(2) The characteristics of the study group's exposure to the substance in question are important. Dr. John Berg (Colorado Regional Cancer Center) said:

" . . . you have to have some idea of the dose that the people are exposed to if you are going to try to attribute the risk to a specific compound.

"Sometimes you may not be able to do this and still find it important to show that there is a risk in a setting. But in general, the aim should be to attribute the risk to something specific, and for that you need the dose." (Berg, Tr. 1677)

Dr. David Wegman (Harvard Univ.) concurred:

"One thing that you need to have is adequate exposure period. It is not adequate to have one year of exposure and Dr. Berg refers in his testimony to the difference between 30 year's exposure in one individual and one year's exposure in 30 individuals, which in our epidemiological way of analyzing, comes out to the same number of person-years, 30, but is very different in terms of what you are likely to find from the two studies if they were elaborated into larger numbers.

"So you need an adequate number of years of exposure, depending on the level of exposure, and I cannot give you a specific guideline except to say that is one of the criteria that has to be evaluated. And the other one is that unless the exposures are very high, that you have to have a reasonable range of exposure in the study population or it will be difficult to distinguish excesses, particularly since it is difficult to come up with good comparison populations; it is better to use—or particularly advantageous to use internal controls at different exposure levels, as indicated by, for example, Dr. Lloyd's study of the coke oven workers where he was able to, by reasonably crude distinctions of exposure levels, identify differential risks associated with exposures.

"So I think you need adequate exposure and a range of exposure within those studies". (Wegman, Tr. 1679–1680)

He pointed out that such data are expecially important in evaluating negative studies based on retrospective data, but are usually not available:

". . . I have yet to see and would be surprised to see adequate, historically collected exposure data to provide us with sufficient evaluation of exposure retrospectively; that is, looking back in time to exposures that have already occurred, to predict that we could come up with, starting today on old data, a negative epidemiologic study that could rule out an association between a given exposure and a risk of cancer that is related to that exposure, because the exposure data is not there." (Wegman, Tr. 1681–1682)

Dr. Umberto Saffiotti (NCI) stated that it is necessary not only to identify the exposure groups but also to define the conditions of their exposure (Saffiotti, Tr. 970). However, this information is rarely available and is often difficult to estimate decades after the fact (Berg, Tr. 1678). Length of employment, although often used as an indirect measurement of exposure, is rarely satisfactory. The only witness who proposed a specific minimum exposure requirement was Dr. Robert Olson (St. Louis Univ.):

"I would say a significant human experience is exposure to a chemical over 20 years, for the purposes of this hearing." (Olson, Tr. 3274)

(3) The length of follow-up of the exposed groups was another widely-discussed issue. Different minimum periods of follow-up have been proposed:

"Negative studies have utility if they are adequate studies, and adequate studies, I think, requires very strict definition. Cancer, as you know, can take up to thirty years to develop after exposure, after even a single exposure. So as a very first criterion you have got to have a study that lasts thirty years". (Rall, Tr. 365)

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"Some of the work that I have done with Phil Cole again indicates that that means around 40 to 50 years. So you are in the position of to identify that 30 percent excess with some sort of—with the usual statistical assumptions of statistical significance and ability not to miss an association that is really there, you would have to follow close to 15,000 exposed people and close to 15,000 controls or comparison individuals for 50 years, just to eliminate the influence of chance." (Hoover, Tr. 794)

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". . . negative epidemiologic data with follow-ups of less than 10 or 15 years are not very useful." (Albert, Tr. 2382)

Dr. Irving Selikoff (Mt. Sinai School of Medicine), referring to studies with asbestos workers, stated:

"We found, for example, that among those less than 15 years from onset of exposure there was very little excess cancer, and there was not a single case of mesothelioma. It was only at 20, 25, 30, 35 years after onset of work that the excess became significant. For example, at 10 to 14 years from onset there was not, as I say, a single mesothelioma. Yet, at 30 years from onset, nine percent of all deaths were due to mesothelioma. There were no cancers of the lung at all in less than ten years from onset of their work, yet at 30 years from onset of their work, one-third of all deaths were due to lung cancer. In other words, the long latent period is striking and is a constraint on all studies of occupational cancers among humans. It must be taken into account.

"If you do not have the opportunity of assessing the mortality experience 30, 35, 40 years from onset, well, withhold any judgment, because that is when for many carcinogens this is found." (Selikoff, Tr. 1697)

Dr. John Berg (Colorado Regional Cancer Center) also agreed that "well over 20 years" is necessary:

"In other words, before a study can be accepted as negative, it must provide at least 20 years of follow-up after exposure (30 years is much better) and every individual exposed must be followed whether they remain on the job, go to other jobs or retire. There must be enough people involved that any appreciable excess risk would in fact provide statistically significant numbers of new cancers. All kinds of cancer must be looked for. A representative group must be studied. Then a negative result will be good evidence that no important hazard exists to the exposed worker." (Berg, S. 24–25)

(4) One also has to be alert to bias in follow-up, a frequent problem. Dr. Berg stated:

"The thing that you should be able to take for granted but unfortunately cannot is that you have complete follow-up of the people and not the tendency that one sees in industry studies very often, to keep track only of the people who stay on the job, who are healthy, who are stable in their employment and stay well, these are the only people that one can follow; therefore, this is the evidence we have to use, and ignore the people who have—particularly those, in some cases, who have retired because of poor health." (Berg, Tr. 1678)

Dr. Roy Albert (EPA) concurred, and added that bias is often difficult to detect. When asked what criteria should be used in evaluating non-positive studies, he replied:

"Whether the people that were doing the epidemiologic study had a vested interest in its being negative . . . or positive. The situation has come up both ways, and I think it is particularly difficult, with all due apologies to industry representatives, for a federal agency to take epidemiologic studies that were done in-house, where it is difficult

to know whether objectivity was used in selecting the individuals included in the study. (Albert, Tr. 2381)

This problem of bias can be somewhat overcome by requiring corroboration of results (or lack thereof) by other studies differing in design or sources of data:

"Comparison of studies differing in design may best be handled statistically (see Section 5). There is a distinct advantage to having the same substance examined by different methods (e.g. case-control vs. cohort) because unrecognized sources of bias or confounding are less likely to operate through both study designs than in replications of a single design. . . Where data from different populations agree, the diversity of source tends to strengthen the association and, presumably, the willingness to generalize the findings to other, untested populations. Where findings differ, sources of bias and confounding must be carefully examined (see 4.2). If discrepancies cannot be so explained, a statistical approach (see Section 5) may be indicated." (Morgan, 1978, p. 9; Hearing Exhibit 218) (See also Dr. Wegman, S. 9).

(5) Another problem is how to define an adequate comparison group. Studies of occupational groups are often confounded by the "healthy worker effect"—the tendency for persons who are actively working to display lower frequencies of disease (including cancer) than otherwise comparable groups in the general population. Hence if cancer mortality or incidence in a group of workers is compared with the mortality or incidence expected in the general population, the standard mortality ratio (SMR) will usually be less than 100 in the absence of any effect of occupational factors (other than the capacity to work *per se*) on cancer mortality or incidence. If a SMR of 100 is observed, this may be *prima facie* evidence of increased risk. The "healthy worker effect" was discussed by Dr. Bo Holmberg (Swedish National Board on Occupational Safety and Health):

"In some epidemiological studies occupationally exposed groups seem to survive longer than the general population. This so-called "healthy worker effect" (McMichael, 1976) is often due to a selection of the workers' population. When an epidemiological study of occupationally exposed people does not reveal an excess risk of cancer—or even reveals a healthy worker effect—this does not prove a lack of effects. Thus epidemiological studies can give "false negative" results. Accordingly exposure to agents known from experimental studies to be carcinogenic should be regulated, even if there is no direct evidence of an excess risk in exposed workers." (Holmberg, S. 10)

Dr. John Berg (Colorado Regional Cancer Center) also described the biases introduced in studies which ignore the "healthy worker effect":

"The most common ploy however is the "healthy worker" study. In one version of this kind of fallacious negative study, only the deaths of workers who are on the payroll at the time of death are tabulated. Workers who retire from illness as well as from age or who just quit because the job made them sick are ignored since the company (fortunately) has no records on these individuals. Given the physical demands of most exposure-prone occupations, it should not be surprising that on-the-job deaths from slowly debilitating diseases such as cancers are rare even when carcinogenic exposures are intense.

"The study of Laws *et al.* (20), cited as proving DDT harmless is a more blatant example of data misuse. In the plant in question there had been 1,098 employees. Of these, 35 who were currently employed were chosen for study. They had absorbed DDT but were healthy. Nothing was done about tracing employees who did not or could not continue work. No comment is made about deaths among the employees. I submit that finding a few people who do not seem to be affected by a substance is far from proving that there is no cancer risk, even if 19 years was long enough to see a cancer risk (and only a few of the 35 men had exposures that long)." (Berg, S. 22–23)

Thus, at the least, an epidemiologic study of workers exposed to a chemical should include matching to a control group of comparable workers if any weight is to be placed on a non-positive result. If such a procedure is not followed, the "healthy worker effect" would invalidate any study which failed to show an excess cancer incidence over that in the general population. Indeed, as Holmberg implied, even a study in which the SMR for workers was found to be 100 may be *prima facie* evidence of excess risk.

On reviewing the expert testimony cited above, OSHA concludes that it is not possible to establish formal criteria for the evaluation of "non-positive" epidemiological studies, and that none have in fact been put forward. As in the case of positive studies, proper evaluation requires the exercise of good scientific judgment, taking into account the factors discussed above. However, it is possible to specify certain *minimum* levels of statistical validity which a study would have to meet before it would be considered as providing any potentially meaningful evidence of an absence of a hazard or risk. These levels, which are based upon substantial evidence in the Record, are discussed below.

d. Examples of allegedly "non-positive" epidemiologic studies for substances giving positive results in animals

The theoretical problems involved in establishing convincing "negative" results in epidemiologic studies would be of less consequence if there were in fact a body of such studies which meet satisfactory scientific standards. A number of witnesses and participants suggested that such non-positive studies do in fact exist. For example, AIHC argued as follows:

"There are physiological and metabolic differences between rodents and man and substances which may be carcinogenic to animals may not be carcinogenic to man. There is evidence in the record that epidemiology can identify substances shown to be carcinogenic in animal tests which do not present a carcinogenic risk to man at the levels to which man is exposed. Dr. Clemmesen and Dr. McLean referred to phenobarbital (Tr. 3553–3556; 4804–4805). DDT and saccharin were cited by Dr. Olson (Tr. 3226). Dr. Golberg referred to dinitrotoluene (Tr. 6511–6513) and DDT and aldrin/dieldrin were cited by Dr. Van Raalte (Tr. 3556–3558, Ex. 53) and Dr. Astolfi (S. at 3–5). Dr. Murray also referred to his extensive practical experience with a number of substances (S. 4)." (AIHC, Post-hearing Brief, p. 127; hearing Exhibit 251)

A number of other witnesses cited DDT and aldrin/dieldrin as demonstrated to be non-carcinogenic in humans (e.g. Lu, S. 7–8; Kotin, Tr. 8730–8731). Dr. Kotin (Johns-Manville) also cited hepatachlor/chlordane and isoniazid (Kotin, S.9). In addition, he and other witnesses cited fibrous glass (Kotin, Tr. 4927, 8758–8760).

Before examining these claims, it is important to note that there is a long historical record of "false negative" epidemiologic studies of chemicals which have later been shown to be carcinogenic in humans. Schneiderman *et al.*, (1978, Appendix D to Schneiderman Post-hearing Comments, Table 2) summarized some of these "false negative" studies. Listed were three reportedly negative studies for arsenic, one for asbestos, two for benzene, one for coke oven emissions, one for petroleum refinery emissions, and two for vinyl chloride. The discussion by Schneiderman *et al.* of the methodological and other reasons for the erroneous findings has already been quoted above (*ibid.*, p. 19–21). In addition, there are other examples of false negative results in the Record, of which the most notable was that of Dr. Irving Selikoff (Mount Sinai School of Medicine), who found no excess incidence of lung cancer in non-smoking asbestos workers for 30 years after exposure. This result was cited by several witnesses at this hearing as evidence that asbestos caused lung cancer only in smokers (Weinstein, S. 7). However after 5 more years' follow-up this result proved to be a false negative (Selikoff, Tr. 1757).

With this warning that non-positive results should be evaluated critically

and with methodological rigor, OSHA has examined the specific claims quoted above.

(1) *DDT*

A number of witnesses who argued that DDT had been shown to be non-carcinogenic cited evidence which is totally unacceptable, even as descriptive epidemiology. Several witnesses argued that liver cancer mortality has been declining in the United States since DDT was first introduced (see, e.g., Lu, S. 8, citing Deichmann and MacDonald 1977). In fact, as discussed above and elaborated upon below, there is no obvious reason why it should be assumed that DDT should act in the liver in humans, rather than at other sites such as the lung or lymphatic system at which it induces excess tumor incidence in mice. In any case, trends in liver cancer have not been uniform. Liver cancer mortality has increased steadily in blacks, especially in black males (Cutler and Devesa 1973). Liver cancer incidence has increased markedly in Connecticut (NAS 1977b, Appendix 10d to Epstein Statement). Dr. Robert Olson (St. Louis Univ.) simply stated: "Despite this widespread distribution and human use, these compounds have not been shown to cause cancer in man" (S. 28). Another witness simply inquired informally of "medical directors" of "manufacturing companies":

"Well, what I did there was again looked at a literature—and that publication really does not mean anything, but then speak with the medical directors or whatever the title may be of large manufacturers of chlorinated hydrocarbon pesticides; a, ask the question, "Are you following this population?" "Yes." "How long have you been manufacturing the material?" "At least two decades." "Have you any evidence of any impact in terms of liver cancer?" (Kotin, Tr. 8730–8731)

OSHA does not believe that it is prudent or scientifically justified to place weight on "epidemiologic" data of this type.

The literature on DDT has been reviewed most recently by NIOSH (1978a) in a publication which included all the references cited by witnesses at the hearing and many others in addition. According to this review:

"DDT has been shown to be carcinogenic in mice in at least 11 experiments, many of which involved exposure for up to six generations, several dose levels or dosage regimens, or several routes of exposure (Table 4.3.2)"

* * * * *

"DDT is carcinogenic in mice, increasing the incidence of tumors primarily in the liver, but also in the lungs and lymphatic system in some experiments. In one experiment, DDT increased the incidence of liver tumors in mice exposed for their lifetime to only 2 ppm in the diet. Tissue levels of DDT in these mice were comparable to or lower than those reported in several studies of occupationally exposed workers. DDD and DDE are also carcinogenic in mice, causing liver and lung tumors; DDE is more effective than DDT itself. In two experiments with rats, DDT induced liver tumors (or "neoplastic nodules") with a low degree of malignancy. DDD has also been reported to be carcinogenic in rats. Three experiments involving exposure to hamsters to DDT have given negative results for carcinogenicity. DDT also interacts with other carcinogens in mice and rats, increasing the incidence of tumors in some experiments and decreasing it in others." (NIOSH, 1978a, pp. 144, 149)

Epidemiologic studies with DDT are complicated by the fact that most general population exposure is to the metabolite DDE, whereas workers are exposed primarily to DDT and to the other principal metabolite DDD; this complication was ignored by some witnesses who argued that "DDT" had been shown to be safe. Only one medium-term study has been carried out with workers exposed to DDT. This study (Laws et al. 1967) was conducted on 35 men employed for 11–19 years, at exposure levels 5–81 times the average for the general population (NIOSH 1978a, pp. 124–125). This study is "inadequate for determining whether DDT may have carcinogenic or teratogenic effects in humans." (*ibid.*, p. 148; see also criticisms of Berg, S. 22–23).

"Workers with mean blood residues of 1.0 ppm (equivalent to a daily intake of about 18mg of DDT) showed a significantly higher frequency of chromatid aberrations than less exposed controls."

* * * * *

". . . Seven studies have been reported in which levels of DDT and DDE in tissues at autopsy have been related to cause of death. In three of these studies, residue levels of DDT and DDE were significantly higher in cancer victims than in persons dying of other causes. No such association was found in the four other studies. Considered in toto, these findings fail to prove or disprove a cause and effect relationship." (NIOSH 1978a, pp. 148, 141)

NIOSH thus regarded the "epidemiologic" studies as inconclusive and made the following recommendation:

"Based on the demonstrated potential of DDT for inducing tumors in both rats and mice, NIOSH recommends that DDT be controlled and handled in the workplace as a suspected occupational carcinogen and that exposure to DDT be minimized to the greatest extent possible." (*ibid:* p. ix).

(2) *Aldrin/dieldrin*

Essentially the same situation holds for aldrin/dieldrin as for DDT. The literature on aldrin/dieldrin has been reviewed by NIOSH (1978b). Aldrin/dieldrin has been shown to be carcinogenic in mice in 20 experiments, increasing the incidence of lung and liver tumors at low doses. Experiments in rats were regarded by NIOSH as "more equivocal":

"In rats, aldrin/dieldrin appeared to increase the incidence of tumors at a variety of sites when administered at low dietary concentrations (0.1–30 ppm), but consistently failed do so when administered at higher concentrations (10–150 ppm). The reasons for this apparent reversal in dose-response relationships are not clear." (NIOSH, 1978b, 105–106).

The only "epidemiologic" study is a survey of a group of only 35 workers who had worked with insecticides, including aldrin and dieldrin, for up to 19 years; their exposure was quite modest, ranging up to about 50 times that in the general population. NIOSH concluded:

"Although a few workers who were exposed to aldrin/dieldrin for up to 19 years have been studied, the available reports are inadequate for determining whether aldrin/dieldrin may have carcinogenic, mutagenic or teratogenic effects in humans. . . .

* * * * *

". . . NIOSH recommends that these two pesticides be controlled and handled in the workplace as suspected occupational carcinogens and that exposure be minimized to the greatest extent possible. (*ibid*: pp. 105, vi).

(3) *Chlordane/Heptachlor*

Despite the claim that while chlordane and heptachlor may cause cancer in test animals and does not in humans (Kotin, Tr. 8730–8731), OSHA is unaware of any adequate epidemiologic study with either or both of these pesticides. (See NAS 1977b, Exhibit 10d to Epstein statement, pp. 20–23).

(4) *Phenobarbital*

Data on phenobarbital were presented by Dr. Johannes Clemmesen (Danish Cancer Registry) and Dr. A. E. M. McLean (AIHC). The data have also been reviewed by IARC (1977, vol. 13, pp. 157–181; Hearing Exhibit 60).

Phenobarbital has been shown to be carcinogenic in the liver in several experiments with mice (Clemmesen S. 16–18 and refs. therein), and in one experiment induced liver tumors ("neoplastic nodules") in rats (Rossi et al., 1977). It interacts with other carcinogens in the liver of rats, enhancing their effects in some circumstances and decreasing them in others (Clemmesen, S. 14–16 and refs. therein).

Dr. Clemmesen presented the results of his own large-scale study of 8078 epilepsy patients who had been treated with anticonvulsant drugs (originally phenobarbital, but subsequently phenytoin) between 1933 and 1962,

followed up to 1972 (Clemmesen, S. 18–20; Clemmesen and Hjalgrim-Jensen, 1977). Three thousand three hundred and forty eight patients were followed for more than 20 years after admission, 2,056 for more than 25 years, and 1,086 for more than 30 years. Excluding brain tumors, which are associated with epilepsy, the only striking result was a highly significant increase in liver cancer (11 observed versus 2.75 expected). Clemmesen attributed this to treatment with Thorotrast, which was verified in 8 of the 11 cases.

Dr. McLean presented the following summary of an unpublished study of epileptics:

"Phenobarbital and Liver Tumors. Unpublished results of a study on people with epilepsy, S. White and A. McLean, 1978. Mortality in 2,000 patients with sever(e) epilepsy, Chalfont Centre, 1951–1974.

	No. Observed	Expected
"Primary Liver Cancer	0	0.5
Deaths from Epilepsy	135	2.2
Accidental Deaths	54	12.5

"Most patients were treated with phenobarbital, but these very severe cases were not adequately controlled by the drug, so that a high mortality resulted in spite of treatment. Without treatment mortality would undoubtedly have been much higher.

"The background level of liver cancer is about 0.5 to one case in 100,000 (age standardized mortality). If the risk were increased by a factor of five to one in 20,000 we might still not detect any cases in about ⅓ of our surveys. But this risk is clearly negligible in contrast to the other risks." (McLean, S. 16–17)

There are several problems involved in accepting these studies as evidence for non-carcinogenicity of phenobarbital:

(i) McLean did not give details of the age, duration of treatment, or duration of follow-up of his patients, so its sensitivity cannot be evaluated. As he himself pointed out, it could have missed the 4-fold increase in liver cancer reported by Clemmesen and Hjalgrim-Jensen, even if the patients had been observed as long.

(ii) Although Clemmesen's study is a model of its kind, epileptic patients (who were partially institutionalized and suffer excess mortality from other causes) are not wholly satisfactory as a study group. Clemmesen observed a substantial increase in respiratory cancer (37 observed vs. 20 expected), which should have been examined against smoking habits in an institutionalized population.

(iii) Clemmesen's explaining away of the positive finding of increased liver cancer, exactly the site expected on the basis of animal experimentation, appears to be *post hoc* rationalization, whether warranted or not. It was criticized as follows:

"Clemmesen did further follow up on these epileptics and found continued excess of respiratory cancers, still a surprise, but not related to the duration of treatment at Filadelfia, thus perhaps not drug related, but only showing the inappropriateness of the measures of "expected" number of cases and an excess of liver cancers, this time statistically significant, and related to duration of treatment (observed as a % of "expected": (less than) 10 yrs. treatment: 153%; (equal to or greater than) 10 yrs: 476%).

"Clemmesen looked at these people still further, and has found that 8 of the 11 patients with liver cancer received Thorotrast, a material that has been associated with liver cancer. To him this is a satisfactory explanation of the dose-response and the statistical significance and he now, neglecting his earlier cautions, asserts that phenobarbitone has proven to be a non-carcinogen in man. I would like to see a consideration of the interaction of phenobarbitone and Thorotrast which this result strongly suggests, a study of thorotrast use in the remainder of the patients, an expectation of liver cancer based on earlier thorotrast experience, and a review of that earlier experience with respect to the use of other interacting drugs (people who were administered Thorotrast usually had rather serious illnesses and it is most reasonable to assume they received other drugs). I find far more unanswered than answered questions in these data.

"To me, converting a statistically significant dose-response effect into *proof* of no effect is a feat in intellectual gymnastics that I must admire, even though I find it hard to accept." (Schneiderman, S. 24)

(iv) Clemmesen's study, if accepted as a negative study of phenobarbital, would also probably be accepted as a negative study of phenytoin, which was given to the patients for at least 20 years. Phenytoin, however, is accepted as a human carcinogen on the basis of other studies (Anthony, 1970; Charlton and Lunsford, 1971; Li *et al.*, 1975; Tomatis, *et al.* 1978).

(v) Subsequent to the hearings, another study with phenobarbital has been published which gave positive results for carcinogenicity (Gold *et al.*, 1978).

Thus Clemmesen's study, despite its relatively large sample size and 35-year follow-up, may prove to be a classical "false negative".

(5) *3,3'-Dichlorobenzidine.*

AIHC (Alternative Proposal, p. 40) cited two studies for the proposition that 3,3'-dichlorobenzidine (DCB) is non-carcinogenic in humans. MacIntyre (1975) surveyed 225 workers thought to have been exposed to DCB in a British plant. Only 12 workers had worked with DCB for more than 15 years, and only 4 for more than 20 years. Only 36 workers had been observed for more than 15 years after first exposure, and only 16 for more than 20 years. No case of bladder cancer was observed. The author commented:

"It is obvious that the majority have been exposed for less than 16 years which means the latent period may not have been reached for all employees . . . Again the majority were exposed within the last 20 years and so there is still time for tumors to appear." (MacIntyre, 1975, p. 24)

Gerarde and Gerarde (1974) surveyed 207 workers presumed to have been exposed to DCB in a U.S. plant. Only 42 workers had worked with DCB for more than 15 years and only 22 for more than 20 years. One hundred one workers were followed up for periods between 20 and 31 years. Twenty-six workers were lost from the study. Seventeen neoplasms had been reported in the group, but no cases of bladder cancer.

Dr. Robert W. Morgan (Univ. of Toronto) stated that:

"I would feel reasonably confident that the negative epidemiological studies of this material makes it unlikely that the substance is a human carcinogen." (Morgan, S. 1)

However, he cited an estimate by the statistician who worked on the Gerarde study that there was one chance in ten of missing a relative risk of 3 [presumably for bladder cancer]. In view of the limited periods of exposure and follow-up, OSHA does not regard this as even weak evidence for lack of risk, and it certainly would not outweigh the positive evidence in rats and mice. On the question of the possible magnitude of the risk, Gerarde and Gerarde stated:

"It is apparent that if DCB is a human bladder carcinogen, it is much less potent than [benzidine] or beta-naphthylamine." (Gerarde and Gerarde, 1974, p. 332)

The basis for this statement is unclear, because no data were presented on the concentrations of DCB to which the employees were exposed (pp. 323–324). Dr. Richard Wilson (Harvard Univ.) attempted to calculate an upper limit for the "potency" of DCB and concluded that the data were consistent with a risk as high as one-tenth that associated with equal exposure to benzidine (Hearing Exhibit 51, Table 1). Thus the fact that excess cancer incidence has not yet been observed in workers exposed to DCB is more likely due to the short periods that have elapsed since exposure, or to the low levels of exposure, rather than to any intrinsic lack of activity or low "potency".

(6) *Isoniazid.*

Isoniazid (INH) has been the principal drug used in the treatment of tuberculosis since the early 1950's. It is carcinogenic in mice and positive in short-term tests (Goldman *et al.*, 1977). Several studies of treated patients have been cited in the record for the proposition that it is nevertheless not carcinogenic in humans (Kotin, S. 9; Grasso, S. 9).

Hammond *et al.* (1967) studied 311 patients followed for up to 15 years after initial isoniazid therapy. There was a small excess of cancer in males (9 cases observed versus 4 expected), which the authors did not regard as significant. Glassroth *et al.* (1977a) reported on 25,323 patients treated with isoniazid in 2 controlled prophylactic trials, and followed up for periods of up to 14 years. The authors pointed out the limitations of such a short follow-up period:

"According to these findings, if INH is conducive to specific types of cancer, the period of observation of the 2 prophylaxis populations is long enough to detect a trend for some types of cancer, but may be completely inadequate for others." (Glassroth *et al.*, 1977a, p. 1072)

No significant excess of cancer deaths was found for any site (*ibid.*, p. 1071). However, there was an unexplained difference between patients in "intensive care wards" and "normal wards", with a marked excess of cancer deaths in isoniazid-treated patients among the former (Goldman *et al.*, 1977). Campbell and Guilfoyle (1970) found no excess of lung cancer deaths in a retrospective study of 3,064 Australian veterans surveyed 8–13 years after treatment with isoniazid. Miller *et al.* (1978) conducted a case-control study of 265 cases of bladder cancer and found an association with prior isoniazid treatment in females. Although the relative risk (3.0) was the highest observed for any risk factor considered in the study, it was not statistically significant because of the small number of cases treated with isoniazid. Glassroth *et al.* (1977b) conducted a case-control study of 142 cases of bladder cancer and 48 cases of renal cancer: none of the cases and only 2 controls had been treated with isoniazid. Stott *et al.* (1976) studied 2,696 patients treated with isoniazid and followed up for 16–23 years. There was no clear association between prior isoniazid treatment and deaths from neoplasms of the lung or other sites. However, the study was complicated by an unexplained change in the incidence of neoplasms during the study. Both patients treated with isoniazid and those otherwise treated after 1953 had excess risks (in the range 1.4–1.8 times those expected in the general population). Since the mean period of follow-up was only 19 years, the authors regarded their findings as provisional (Stott *et al.*, 1976, p. 12).

Although these six studies were extensive and well-conducted, their limitation, with one exception, to follow-up periods of 8–15 years makes them of very limited value as evidence for non-carcinogenicity of isoniazid (see quotations above; Goldman *et al.* (1977, pp. 470, 472); Kotin and Chase, Tr. 8730). Even if the short follow-up periods are discounted, there are some suggestive positive findings in at least two of the studies. Moreover, with the exception of the study by Glassroth *et al.* (1977b), all the studies were conducted on treated tuberculosis patients, and are likely to have been complicated by interactions between tuberculosis, lung cancer, and smoking habits (Stott *et al.*, 1976).

(7) *2,4-Dinitrotoluene.*

OSHA is not aware of any epidemiologic studies conducted with 2,4-dinitrotoluene (see Goldberg, Tr. 6513–6514).

(8) *Fibrous glass.*

Studies relevant to assessing potential risks associated with exposure to fibrous glass have been reviewed by NIOSH (1977a). Fibrous glass induces tumors (sarcomas and mesotheliomas) in animals exposed via intrapleural or intraperitoneal implantations. The effects are much greater for long, thin fibers (less than 0.25 μm in diameter and longer than 8 um in length) (Stanton *et al.*, 1978). Unlike asbestos, glass fibers have not been shown to be translocated to the pleura or peritoneum after inhalation. Fibrous glass is less effective in inducing tumors in animals than asbestos.

"Much of the concern about fibrous glass results from certain similarities with asbestos. Both are fibrous materials of varying lengths and diameters. The diameters of glass fibers are generally larger than those of asbestos fibers. Asbestos fibers and fibrils are most often less than 1 μm in diameter. The asbestos fibers tend to fracture longitudinally to form fibrils less than 0.5 μm in diameter. Fibrous glass was found to clear more rapidly than anthophyllite asbestos in a comparative study of single inhalation exposures [59]. Similarities in fibrogenic response between fibrous glass and asbestos have been observed from intratracheal studies in rats but the response was quantitatively less with fibrous glass [64]. Both fibrous glass and asbestos acted quite similarly in the various lesser incidence of tumors." (NIOSH, 1977a, p. 93)

Two studies of workers exposed to fibrous glass have involved sufficiently long follow-up to merit review. Enterline and Henderson (1975) studied 416 workers who had retired after unspecified periods of work with fibrous glass. Workers who had died before age 65 were not considered. Among workers who retired, there was a non-significant increase in "non-malignant diseases of the respiratory system". Bayliss *et al.* (1976) conducted a retrospective cohort analysis of 1448 workers with 5 or more years' exposure to fibrous glass and follow-up for 23–32 years after initial employment. There was a significant excess of deaths due to "nonmalignant respiratory diseases" (19 observed vs. 10.04 expected). The workers were apparently exposed to very low airborne concentrations of glass (0.08 fibers/ml). The median diameter of the fibers was 1.8 μg and the median length 28 μm. A subgroup of workers thought to have been exposed for limited periods to smaller fibers (1–3 μm diameter) showed a marginally significant excess frequency of deaths from "malignant and nonmalignant respiratory disease". [This conclusion has been disputed: see comments of Kotin and Chase (Johns-Manville), Hearing Exhibit 181]. Neither the study of Enterline and Henderson (1975) nor that of Bayliss *et al.*, was controlled for smoking.

NIOSH concluded:

"On the basis of the information available for evaluation, fibrous glass is not at this time considered to present a carcinogenic hazard in the workplace." (NIOSH, 1977a, pp. 92–93)

However, this conclusion would apply at best to the larger fibers to which most workers were exposed in the past. Strong positive results in animals have been obtained only with smaller fibers (Stanton *et al.*, 1978), and indeed it is questionable whether the large fibers are carcinogenic in animals at all. Bayliss *et al.*, pointed out:

"However, because commercial production of small-diameter (less than 1 μm) fibers only began in the 1960s, no facility has been in operation sufficiently long to permit evaluation of the manifestation of any potential pathogenic lung effects, including carcinogenicity, that result from inhalation and exposure to small-diameter glass fibers." (Bayliss *et al.*, 1976, p. 330)

In view of the low exposure levels and the marginal positive finding by Bayliss *et al.* (1976) the available studies are not strong "non-positive" evidence, even for the large diameter fibers. There is also a question of the appropriateness of the route of exposure, since positive animal results have been obtained only by intrapleural or intraperitoneal implantation, and it is not clear whether inhaled fibers are translocated systemically to these tissues. These points should be explored more fully in a rule-making proceeding on fibrous

glass or subcategories thereof. For the purposes of this generic rule-making, the available studies do not constitute persuasive evidence that the animal studies are not relevant to the prediction of human hazard for the specific types of fiber tested: the epidemiological studies are not directly relevant and in any case are not conclusively negative. Thus the data on fibrous glass do not provide a good example of a case in which a "non-positive" epidemiological study should outweigh positive animal data. Indeed, substantial evidence in the Record supports the proposition that such a study should be outweighed by positive animal data.

(9) *Saccharin.*

Dr. Robert Olson (St. Louis Univ.) cited 8 published epidemiologic studies and a review by Wynder and Weisburger (1977) for the proposition that:

". . . there is no reliable evidence of any increase in any tumors in those groups using sweeteners extensively as compared to non-users." (Olson, S. 27)

These and other epidemiologic studies have been reviewed in detail by a Committee of the National Academy of Sciences established specifically to review the data on saccharin. This committee found "many deficiencies" in the studies cited by Dr. Olson, and discussed in detail two less deficient studies published subsequently:

"The committee reviewed the epidemiologic studies of the relationship between saccharin and bladder cancer and between saccharin and spontaneous abortion. With one exception, findings indicated the absence of a health hazard for either sex. However, there were many deficiencies in the methods of the studies that showed no association.

(1) Time-trend studies by Armstrong and Doll in 1974 and by Burbank and Fraumeni in 1970 provide no evidence that saccharin use is necessarily associated with cancer. This method may be too insensitive to separate the effects of saccharin from known bladder cancer risk factors, such as cigarette smoking, that have been changing over time.

(2) Studies on diabetics, by Armstrong *et al.* in 1976, by Armstong and Doll in 1975, and by Kessler in 1970, do not show a positive association between saccharin use and bladder cancer, but these studies suffer from a number of limitations that hinder assessment of the risk of saccharin: (a) findings in diabetics may not be applicable to the nondiabetic population; (b) individual saccharin consumption was not measured; and (c) there were no data on smoking habits and certain occupations that are known to be associated with bladder cancer.

(3) The case-control studies do not provide clear evidence to support or refute an association between saccharin use and bladder cancer. Two studies of sufficient size for reliable measurement of low-level effects of saccharin use are those by Howe *et al.* in 1977 and by Kessler and Clark in 1978. The study by Howe *et al.* used a complex method to estimate the relative risk of bladder cancer in nonnutritive sweetener users and non-users. This study reported that the proportion of male bladder cancer patients who used nonnutritive sweeteners is significantly higher (risk ratio of 1.6) than the proportion of male controls who used nonnutritive sweeteners. The study by Kessler and Clark reported no statistically significant excess risk for either sex, and is thus consistent with no excess cases of bladder cancer attributed to the use of saccharin. The committee believes that the methodologic difficulties of each study do not allow one to judge the seemingly contradictory results. Four other case-control studies—those by Kessler in 1976, Morgan and Jain in 1974, Wynder and Goldsmith in 1977, and Simon *et al.* in 1975—have failed to demonstrate a statistically significant risk, but these studies have major deficiencies which severely limit confidence in their findings." (NAS, 1978, pp. TS–4–5)

The Committee summarized its findings as follows:

"The epidemologic studies that are detailed in Chapter 3 do not provide clear evidence to support or refute an association between past saccharin use and bladder cancer in males. All but two of the studies either suffered from methodologic difficulties or were too insensitive for reliable measurement of a potentially low-level effect of saccharin use. Of the two most extensive studies, one shows a statistically significant excess number of cases of bladder cancer; the other does not." (*ibid.*, p. ES–6, emphasis in original)

Dr. Robert Hoover (NCI) had earlier pointed out that if the experimental data on saccharin carcinogenesis in rats were extrapolated to predict the magnitude of human risk, a relative risk of about 1.04 would be expected for bladder cancer, far too low to be detected. However, the study of Howe *et al.* (1977) indicated a much larger risk (Hoover, Tr. 789–791). In view of these findings, the epidemiologic data on saccharin are at best inconclusive; there is a strong possibility that saccharin, too, will prove to be a classical "false negative".

(10) *Summary*

In summary, none of the examples of "non-positive" epidemiologic studies cited by participants to this rulemaking can be accepted as evidence of non-carcinogenicity. Indeed, several appear likely to prove to be classical "false negatives".

7. Use of Epidemiologic Studies To Set Upper Limits of Risk.

Although there was thus little evidence in the Record that epidemiologic studies have established satisfactory evidence of non-carcinogenicity for any substance,* another potentially important function of epidemiologic studies was suggested by several participants. As quoted above, the NCAB Subcommittee pointed out that:

Negative data on a given agent obtained from extensive epidemiologic studies of sufficient duration are useful for indicating upper limits for the rate at which a specific type of exposure to that agent could affect the incidence and/or mortality of specific human cancers. (NCAB Report, 1977, p. 462)

Several parties to the hearing recommended that OSHA should in fact use "negative" data in this way. For example, API argued as follows:

Many witnesses testified that there may be cases where, through an exercise of scientific judgment, it is apparent that the negative results have significant bearing on carcinogenic risk. Dr. Albert, for example, testified that evidence based on several sound negative studies and one marginally-adequate positive result represents a weaker basis for regulation than do two sound positive studies and several marginally-adequate negative ones. Further, EPA considers negative epidemiologic data to be an indispensable regulatory tool in "provid[ing] an upper limit of how bad the agent could be." (API, post hearing Brief, p. 36, citing Dr. Albert, Tr. 2336–2337, 2378–2380)

AIHC argued as follows:

"Negative epidemiology can also serve to correct risk estimates based on positive animal data. Perhaps the best example in this record is ethylene dibromide where on the basis of an epidemiological study of 158 exposed workers, EPA was led to modify its risk assessment from exposure to that compound based on positive animal data. (Ex. 43, Tr. 2336; "Risk Assessment for Ethylene Dibromide (EDB)," API P.H.) EPA also testified that negative epidemiological data are particularly useful where a positive animal study involves a route of exposure different from human exposure. (Tr. 2383)

"Another example in the record of the use of human epidemiology to adjust or correct a risk assessment based on animal data is the FDA risk assessment of aflatoxin in peanut butter. (Ex. 38.) The FDA relied on epidemiological data in reaching the conclusion that humans are biologically closer to aflatoxin resistent [sic] mice than the more aflatoxin susceptible rats. *Id.* at 3–4. The data were also used to calculate the potential health benefits from an additional reduction in aflatoxin level. *Id.*

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* The Report of the Safe Drinking Water Committee cited extensive cross-sectional studies of populations exposed to fluoridated and non-fluoridated drinking water in support of the proposition that fluoride at therapeutic levels is non-carcinogenic (NAS, 1977a, pp. 381–389). These studies are among the most extensive ever undertaken and provide better evidence of non-carcinogenicity (or of very low risk) than any others in the record of this hearing. However, they have little relevance to occupational exposure. They do not, for example, exclude the possibility of risks from cancer to workers exposed to fluorides by inhalation.

The record does not support OSHA's administrative rejection of negative human studies. On the contrary, the record makes clear that such studies can have significant value. (AIHC Post-hearing Brief, pp. 127–128)

AIHC also cited (*ibid.*, p. 126) Dr. Bates (NIEHS) (S. 11) and Dr. Hoover (NCI)(Tr. 794) in support of this proposition.

DuPont also suggested in a less specific comment that epidemiologic data could be used in this way to set an "acceptable level of exposure":

We submit that an acceptable level of exposure is one which gives high confidence that there will be no observable excess of cancer in the population at risk due to occupational exposure to chemicals. It does not assure that no cases will occur, but it does provide confidence that such cases, if any, will be well below the variation in cancer from other causes (e.g., diet and cigarette smoking) and thus undetectable.

Criteria for determining an acceptable level of exposure from epidemiological data. An acceptable level of exposure can be determined from valid epidemiological data where there is adequate data about previous exposure levels among the cohort. The DuPont Recommended Alternative (Appendix A) contains a list of criteria which should be used in evaluating the validity of epidemiological data." (DuPont, S. 26)

In its post-hearing brief, DuPont observed:

"Perhaps the clearest statement of the role of negative epidemiology is in the Report of the Subcommittee of the National Cancer Advisory Board entitled "General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances." In this very careful report subject to extensive peer review, the Committee concluded:

" 'Negative epidemiological data may not establish the safety of suspected materials. Negative data in a given agent obtained from extensive epidemiologic studies of sufficient duration are useful for indicating upper limits for the rate at which a specific type of exposure to that agent could affect the incidence and/or mortality of specific human cancers. NCAB General Criteria at 462.'

"Dr. Rall agreed with the NCAB as to the appropriate role for epidemiology (Tr. 366). Dr. Hoover and Dr. Bates also agreed that a valid negative study could identify the upper boundary of a potential hazard (Tr. 794; Bates S. 11). Dr. Berg urged OSHA not to reject a valid negative study (Tr. 1679). Even Dr. Epstein testified that negative studies should be weighed in the regulatory process (Tr. 1462)." (DuPont, Post-hearing Brief, p. 18; Hearing Exhibit 267)

DuPont concluded:

"Epidemiology is properly used to identify the human risk. Negative epidemiology is useful to indicate upper limits for the rate at which a specific type of exposure to that agent affect the incidence and/or mortality of specific human cancers."(ibid., p. 27)

However, while the idea that epidemiologic studies may be used to establish upper limits of risk may be conceptually sound and theoretically attractive, the examples presented in the Record were not very convincing and do not suggest that this proposed method would be very useful in standard-setting. OSHA does not reject such an approach, however, as discussed below, but points out that better epidemiologic studies are needed to utilize this approach than were available in the cases cited.

In the case of ethylene dibromide, EPA indeed revised its estimate of potential risks extrapolated from a carcinogenesis bioassay in rodents, on the basis of a "non-positive" study in occupationally exposed workers. However, the rodent bioassay was one which had raised unusually difficult problems of extrapolation: the induction of stomach tumors in rats after administration by gavage was used to predict possible induction of cancer at unpredictable sites in humans after exposure by inhalation. Hence the fact that the observations in humans were inconsistent with the high estimate of risk derived from the animal data is of little significance except to emphasize the uncertainties involved in extrapolating across different species, routes, and organs (see below in the section on Quantitative Estimation of Risk). The unpublished "epidemiologic" study referred to by API and AIHC was apparently no more than a mortality survey. As presented in Hearing Exhibit 43, only 156 workers were involved, who were exposed to low concentrations of ethylene dibromide (0.9–3.0 ppm TWA) for unspecified periods (which were presumably only a limited part of a lifetime, since the average age of the workers at the time of study was only 55 years). No mention is made of the completeness of follow-up of former employees. Nevertheless at one plant an excess of cancer was actually observed (5 cases observed versus 2.2 expected, which the authors state was not statistically significant, but in fact was significant if allowance is made for the healthy worker effect). Considering the limited fraction of a lifetime involved in the study, the data are consistent with a 5–10 fold increase in lifetime risk even at the low exposure levels involved.

For aflatoxin, OSHA has studied the FDA document proffered by AIHC (Hearing Exhibit 38) and does not agree that it provides unequivocal support for the proposition that "humans are biologically closer to aflatoxin resistent (*sic*) mice than the more aflatoxin susceptible rats." Apart from uncertainties and qualifications actually presented by FDA, there is in fact little difference in the susceptibility of rats and mice to aflatoxin—no more than a factor of 4–10 according to Wilson (Hearing Exhibit 51, Table 1, citing data analyzed by Meselson and Russell 1977). According to AIHC's own witness, Dr. Richard Wilson, citing data from the same paper by Piers and Linsell (1973) as that on which FDA's analysis was based, humans fall approximately between rats and mice in their susceptibility (Wilson Hearing Exhibit 51). Other experts who have analyzed human and animal data on aflatoxin-related liver cancer also found that humans and rats were quantitatively similar in susceptibility, within the limits of reliability of the data (see e.g., NAS, 1975a, p. 51).

There are data in the record for four other carcinogens for which similar calculations might be performed. Dr. Richard Wilson (Harvard Univ.) presented upper limits on the "potency" in humans of two carcinogens for which he regarded the epidemiologic evidence as negative. These were saccharin and 3,3'-dichlorobenzidine (Wilson, Hearing Exhibit 51, Table 1). However, for saccharin Wilson's estimate of the upper limit of "potency" (and hence the upper limit on low-dose risk) was 20 times higher than that for rats. For 3,3'-dichlorobenzidine the upper limit on "potency" was 400 times higher than that for mice. Hence the human data are of no value whatsoever for establishing an upper limit on risk that would be lower than that predicted on the basis of animal experiments.

For two other carcinogens, vinyl chloride and diethylstilbestrol (DES), data on human carcinogenic response were judged to indicate lower susceptibility than data on mice and rats (NAS, 1975a, p. 51). Hence, if the human data are regarded as complete measures of response, they could be used to establish risk levels lower than those extrapolated from the animal data (see Wilson, Response to Post-hearing Comments of Nisbet, pp. 8–10). However, as the NAS Committee pointed out (NAS, 1975a, p. 82), the data on vinyl chloride and DES are for rare tumors exhibited after short latent periods. In the case of vinyl chloride, there is already evidence for excess risks of cancer at other sites. In the case of DES, OSHA is well aware that there are millions of young people in the United States who were exposed to DES *in utero*, and that many of them exhibit tissue abnormalities which may develop into cancer later in life. It will be more than 50 years before this unfortunate "experiment" is concluded and we are

able to determine the "upper limit" on their risk.

Thus, OSHA is not aware of a single case in which "negative" human epidemiological data could be used reliably to establish upper limits on risk. In particular, OSHA is unaware of reliable data for any carcinogen that would demonstrate that the upper limit on risks to humans is below the risks measured in animals under comparable exposure conditions. However, if such data become available and are presented in rulemakings on specific substances, OSHA is certainly prepared to rationally and responsibly use them in attempting to establish low dose risks. Guidelines for minimum standards for consideration of "non-positive" epidemiological studies are set out below. To be useful in standard-setting, such studies would also need to be accompanied by quantitative data on exposure histories. However, OSHA's experience to date is that such data are often a matter of uncertainty and dispute (e.g. in the benzene rulemaking). For this reason, OSHA is unlikely to be able to use such data unless the circumstances of exposure are well-defined, so that the magnitude of the calculated "upper limit" on risk can be calculated accurately.

C. OSHA'S CONCLUSIONS

On the basis of a review of the extensive evidence in the Record, OSHA draws the following general conclusions:

1. Retrospective epidemiologic studies of exposed workers are very difficult to carry out in a systematic and unbiased manner, and in fact comparatively few good studies have been reported.

2. Epidemiologic studies are complicated by many factors, including the selection of exposed and control groups, definition and measurement of exposure, length of exposure and follow-up periods, and various kinds of bias.

3. If care is taken to minimize biases, positive results in epidemiologic studies are an important source of information on hazards to exposed workers.

4. Although specific criteria for the conduct and evaluation of epidemiologic studies cannot be laid down, there is widespread agreement on the factors to be considered in evaluation of studies. The most important requirement is the exercise of informed scientific judgment.

5. "Non-positive" epidemiologic studies cannot, in principle, establish the safety of agents under suspicion on other grounds. None of the studies presented as "non-positive" in this rulemaking stands up to critical scrutiny.

6. In theory, "non-positive" epidemiologic studies may serve to establish upper limits on potential risks under specified conditions of exposure. However, the few examples of such calculations presented in the Record are not convincing.

Accordingly, OSHA believes that substantial evidence in the Record supports the following specific conclusions:

1. That scientifically evaluated positive evidence for carcinogenicity of a substance in humans should serve as the basis for the classification of a substance as a potential occupational carcinogen. The general provisions of the OSHA Cancer Policy therefore state (1990.143(a)):

> "(a) *Positive human studies.* Positive results obtained in one or more human epidemiologic studies will be used to establish the qualitative inference of carcinogenic hazards to workers."

2. That, in general, positive animal data should supersede "non-positive" human data in the qualitative identification of a hazard, as will be discussed below.

3. That epidemiologic studies, if accompanied by reliable data on exposure levels, may be useful in priority-setting, but are rarely, if ever, sensitive enough to be useful in setting acceptable levels of exposure.

OSHA recognizes that exceptions to these general rules may arise in specific cases. No such cases for such exceptional treatment were presented in the Record, however. Accordingly, OSHA believes that such exceptional cases, if they should arise, should be treated as exceptions in the manner specified below, rather than through any modification to the general policy. In this manner, the policy itself provides that OSHA will evaluate all meaningful and relevant evidence, including evidence that provides "non-positive" results.

Based on the testimony and evidence in the Record, and the desire for needed scientific flexibility in reviewing the relevant data, as pointed out below, OSHA believes that epidemiologic studies which give "non-positive" results will rarely provide evidence to offset scientifically evaluated positive results of carcinogenicity observed either from other human studies or from experimental studies in test animals. Hence OSHA will not, in general, consider such non-positive studies in the qualitative identification of a carcinogenic hazard, either in classifying potential occupational carcinogens or in weighing evidence offered as exceptions to the general policy. However, OSHA recognizes that there may be circumstances in which the results of positive studies in humans or in animals may be less than convincing or conclusive and which may, in fact, be substantially offset by "non-positive" results in an extensive epidemiological study. Likewise, although none of the cases presented in the hearing to support this proposition was convincing, it may be possible in theory that the results of epidemiologic studies could be used to establish upper limits on risks, provided that sufficient data are available on exposure levels. For these reasons, OSHA has reviewed the evidence in the Record and has used it to establish minimum criteria for determining whether and in what circumstances such evidence should be considered for assessing risks, either qualitatively or quantitatively. OSHA's purpose in establishing these criteria is to encourage the collection of good epidemiologic data and to use such data responsibly when they provide cogent evidence on risks, while avoiding wasting time and resources on consideration of inadequate or limited data which do not provide such evidence.

While meeting these minimum criteria only permits the party introducing the evidence to argue its relevance before the Agency, OSHA believes that prudence in the interest of public health dictates that the evaluation of such evidence should await the case-by-case rulemaking. However, OSHA believes that in light of the insensitivities of non-positive epidemiologic studies and other matters discussed above, the minimum criteria set forth at least the reasonably necessary minimum requirements that should be met before any exception promulgated in this set of regulations, should be considered by OSHA in the future. Thus, the OSHA Cancer Policy provides (§ 1990.143(c)):

> "(c) *Non-positive human studies.* Positive results in human or mammalian studies generally will be used for the qualitative identification of potential occupational carcinogens, even where non-positive results from human studies exist. Such non-positive results will be considered by the Secretary only if the studies or results meet the criteria set forth in § 1990.144(a)."

Specifically, the minimum criteria, found at 1990.144(a), are:

> (a) *Non-positive results obtained in human epidemiologic studies.*
>
> Non-positive results obtained in human epidemiologic studies regarding the substance subject to the rulemaking or to a similar or closely related substance will be considered by the Secretary only if they meet the following criteria.
>
> *Criteria.* (i) The epidemiologic study involved at least 20 years' exposure of a group of subjects to the substance and at least 30 years' observation of the subjects after initial exposure;

(ii) Documented reasons are provided for predicting the site(s) at which the substance would induce cancer if it were carcinogenic in humans; and

(iii) The group of exposed subjects was large enough for an increase in cancer incidence of 50% above that in unexposed controls to have been detected at any of the predicted sites.

The first criterion is related to the duration of the epidemiologic study. There was ample evidence in the Record that epidemiologic studies do not provide any useful evidence of lack of hazard or risk unless they represent studies of the consequences of exposure extending over 20–30 years or more. On the basis of the evidence in the Record and the specific statements reviewed above, OSHA concludes that the Record amply supports the proposition that epidemiologic studies that are purportedly "non-positive" should not be considered unless such studies involve a minimum of 20 years exposure of workers or other subjects to the substance and a minimum of 30 years' follow-up after initial exposure. For example, the criterion of 20 years' exposure was discussed by Mr. Peto (Peto, Tr. 2452) and Dr. Olson (Olson, Tr. 3274), and that of 30 years' follow-up is based upon the discussion of this issue by the IARC (1978, Vol. 17, p. 19) and the testimony of Dr. Selikoff (Selikoff, Tr. 1697, 1757), Dr. Rall (Rall, Tr. 365), Dr. Hoover (Hoover, Tr. 794) and Dr. Berg (Berg, S. 24–25). Although some of these witnesses argued that 40 or even 50 years of follow-up was necessary before clear inferences of a negative could be drawn, OSHA believes that 30 years can reasonably be used as a criterion to allow the *consideration* of studies which provide evidence of some limited value.

The second criterion is related to the site at which cancers may be induced. As pointed out by Dr. Berg, an epidemiologic study cannot be said to be negative unless *all* cancer risks are shown to be acceptable (Berg, S. 23–24). Thus, in theory at least, an epidemiologic study must be sensitive enough to detect a 50% increase in cancer incidence at *any* site before it can provide really cogent evidence of lack of risk. In practice, such a criterion could not be used, because no epidemiologic study of practical size could detect a 50% increase in a rare type of tumor. Thus, OSHA is willing for practical reasons to consider studies which are sensitive enough to detect a 50% increase at all sites where the agent is judged likely to act in humans. The third criterion, then, is that documented reasons should be provided for predicting the site(s) at which the substance is likely to induce cancer if it were carcinogenic in humans. For the reasons stated by Dr. Berg, it will not, in general, be sufficient to assume that a substance would act in the same site in humans as in animals: additional evidence such as the site-specificity of structurally related compounds would normally be required.

The third criterion is concerned with the sensitivity of the study to detect effects which may be judged to be significant. As discussed in Section B.6 above, the sensitivity of an epidemiologic study (assuming it is well conducted and free of biases) is determined primarily by the size of the study population and its background incidence of cancer. Several witnesses pointed out that even relatively large studies are often barely sensitive enough to detect a five-fold increase in risk (see testimony of Dr. Nicholson, Tr. 1756, and Dr. Selikoff, Tr. 1757). Dr. Bates (NIEHS; FDA) testified that few studies have been of sufficient sensitivity to detect anything smaller than a 50% increase in the incidence of cancer over that found in the general population (Bates, S. 7). Dr. Hoover (NCI) testified that the smallest excess risk established to date in an epidemiological study is between 30% and 40% (Hoover, Tr. 789–790) and that epidemiologic techniques cannot be expected to detect excess risks of 5–10%.

This testimony presents OSHA with a dilemma. An excess risk of 50% can hardly be regarded as negligible, especially in view of OSHA's statutory mandate to assure "that no employee will suffer material impairment of health or functional capacity . . .". Therefore, OSHA has concluded that it would be justified to require, prior to consideration of evidence showing a "non-positive" result, that any study showing such results be capable of detecting at least a 50% excess risk in exposed humans. Although it is questionable whether such a study would in fact provide the "assurance" required by the Act, the testimony of Dr. Hoover and Dr. Bates suggest that to require greater sensitivity would place unreasonable demands on the epidemiologic technique. And to require proof of "absolute negativity" would be impossible. Thus, OSHA believes that this criterion is a reasonable compromise between the limited sensitivity of epidemiologic studies and the extreme sensitivity required to provide adequate assurance of minimal adverse effects.

If non-positive results of an epidemiologic study are to be used as the basis for establishing upper limits on risks at specific exposure levels, the considerations discussed above relative to duration of the study and the prediction of the site of action are equally valid. Hence, OSHA intends to require the first and second criteria stated above as minimum criteria to be met for the consideration of evidence from such studies. If these criteria are met, the results of the study may be used to calculate statistical upper confidence limits on the risks experienced by the workers included in the study. However, these upper confidence limits will only be of value in establishing a relationship between upper limits on risks and exposure levels if there is precise information on the level of exposure of the study population. Accordingly, OSHA will establish as an additional criterion for the consideration of such data the requirement that specific data on the level of exposure of the study population be provided. Such data must be based either on direct measurements of exposure levels made periodically throughout the period of exposure, or upon other data which provide unequivocal evidence of the magnitude of exposure.The relevant portion of § 1990.144(a) provides that:

Arguments that non-positive results obtained in human epidemiologic studies should be used to establish numerical upper limits on potential risks to humans exposed to specific levels of a substance will be considered only if criteria (i) and (ii) are met and, in addition:

(iv) Specific data on the level of exposure of the group of workers are provided, based either on direct measurements made periodically throughout the period of exposure, or upon other data which provide reliable evidence of the magnitude of exposure.

PART C.

V. EVIDENCE DERIVED FROM EXPERIMENTAL LONG-TERM BIOASSAY RESULTS IN MAMMALIAN LABORATORY ANIMALS

A. OSHA'S PROPOSAL

In the preamble to the proposed regulation, OSHA placed great reliance upon positive results arising from long-term animal experimentation to qualitatively identify potential occupational carcinogens. As proposed, a positive finding in one or more mammalian test species was considered sufficient evidence upon which to initiate some type of regulatory action under section 6(b) of the Act. Specifically, the definition of "potential occupational carcinogen" proposed was:

". . . any toxic substance which (1) [c]auses, at any level of exposure or dose, as the result of any oral, respiratory or dermal

exposure, or any other exposure which results in the systemic distribution of the substance under consideration, in the organism tested, an increased incidence of benign or malignant neoplasms, or a combination thereof, in (i) humans or (ii) in one or more experimental mammalian species, or (2) in a statistically significant manner decreases the latency period between exposure and onset of neoplasm in (i) humans or (ii) in one or more experimental mammalian species." (42 FR 54184)

As pointed out above, for practical purposes the detection today of carcinogenic activity of most substances is based on experimentation in laboratory animals. All substances or mixtures of substances that have been proven carcinogenic by direct observation in humans have also been shown to be carcinogenic in experimental animals (with the exception of arsenic and perhaps benzene, still under experimental study). Because of the difficulties of epidemiologic studies of humans exposed to potential carcinogens, OSHA recognized that there may be no data which provide absolutely definitive evidence—one way or another—as to whether cancer is caused in humans by a substance that has been shown to be carcinogenic in test animals.

OSHA stated, however, that the failure to assume that such a substance does pose some level of carcinogenic threat to humans seemed imprudent and could lead to a public health disaster. OSHA quoted the "expert" Ad Hoc NCI Committee's report to the Surgeon General which stated in 1970:

"Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard for man." (NCI Ad Hoc Committee, 1970, p. 1; Exhibit 10b to Epstein Statement)

B. THE PUBLIC'S RESPONSE

Virtually all witnesses and participants agreed that evidence and data derived from experimental studies in mammalian test animal species should be relied upon by OSHA to identify a hazard to humans. However, a dichotomy developed on this issue as between substances to which humans are presently exposed and those "new" substances to which no humans are exposed and which presumably can be regulated without incurring great economic costs. Most, if not all, witnesses agreed that as to these latter substances, animal evidence alone should serve as the basis for regulatory action, although other witnesses and industrial groups suggested that regulatory action should not be initiated for the former substances until conclusive positive human data are available.

A number of distinguished scientists who testified at the hearings expressed opinions supporting OSHA's proposed position. Dr. Arthur Upton (Director, NCI) testified as follows:

"When a chemical substance (or mixture) is found to be carcinogenic in animals, it is prudent to assume that it has at least the potential to induce cancer in humans also. This assumption is accepted by the vast majority of experts in chemical carcinogenesis, and indeed underlies most of the experimental work in the field. As documented in the preamble to OSHA's proposal, it has also been enunciated explicitly by several expert international and national committees. It rests upon the following body of experience:

"1. All the chemicals demonstrated to cause cancer in humans, with the probable exception of arsenic, are known to cause cancer in animals, although they often act at different sites.

"2. Most chemicals shown to induce cancer in one mammalian species also induce cancer in other mammalian species when properly tested. Although there is often much variation in susceptibility from one species to another, there are few, if any, adequately-documented cases of species-specific carcinogens.

"3. The pathological development of tumors in various species of animals, including man, is similar; there are laboratory animal models for most types of human cancer.

"4. There is evidence that the mechanisms of molecular interactions of many carcinogens with target cell macromolecules are the same in several animal species and in humans. At this fundamental level of biological organization, there is no reason to expect qualitative differences in response between species."

* * * * *

"Given this lack of knowledge concerning mechanisms, I believe that a reproducible carcinogenic response in any species of test animals must be considered sufficient to describe the test compound as a carcinogen and so a potential threat to human health . . ."

". . . Given the variation in human susceptibility to carcinogens, I believe it unreasonable to ignore a finding of carcinogenicity in any mammalian test species when considering possible effects on human health." (Upton, S. 12–13, 17)

Later, in response to questioning on the subject, Dr. Upton added:

"I would think that the mere evidence of carcinogenicity in animals is sufficient to label the compound as a potential carcinogen for humans." (Upton, Tr. 330)

Dr. David Rall (Director, NIEHS) testified as follows:

"There are several reasons why the assessment of the carcinogenic risks of industrial chemicals must be based primarily on animal experimentation rather than on direct observation of carcinogenic effects in man. First, as pointed out above, very few industrial chemicals and processes have been subjected to adequate epidemiological studies to determine whether or not they cause carcinogenic effects in workers. Second, epidemiological studies are insensitive and little weight can be placed on surveys which do not show positive results. Third, many industrial chemicals have not been in production long enough for any effects to be observable, bearing in mind the long latent periods for chemically-induced cancers. Fourth, it would be unethical to wait for evidence of harm in exposed workers when risks can be established relatively quickly by animal experimentation." (Rall, S. 6–7)

This testimony echoed many of the same arguments voiced by OSHA in the proposal. Dr. Rall was also very emphatic on this point in his oral testimony:

"I think the evidence is overwhelming that if you have got a good, positive study in animals, regulatory action should flow from there." (Rall, Tr. 423)

Dr. Donald Kennedy (Commissioner, FDA) expressed his approval of OSHA's use of animal experimentation in the identification of potential human carcinogens:

"The OSHA proposal contains the statement that substances determined to be carcinogenic in mammals will be treated as a *policy matter* as posing a carcinogenic risk to humans. Based on what I have said above, I would take the position that this principle need not be only a matter of policy. It is a scientifically justifiable principle." (Kennedy, S. 10)

Dr. Richard Griesemer (NCI) stated:

"The most logical and scientifically sound approach to identifying chemical carcinogens is through animal experiments . . . With the presently available data, it must be presumed that those chemicals that cause cancer in animals are potentially carcinogenic for man." (Griesemer, S. 5–6)

Dr. Umberto Saffiotti (NCI) testified on this subject as follows:

"Another major reason for accepting evidence of carcinogenicity from experiments in mammalian species is the large body of knowledge that has accumulated for decades, and particularly in the last decade, on the comparative pathology of human and experimental cancers demonstrating their close similarity on both morphological and functional grounds." (Saffiotti, S. 20–21)

Dr. Saffiotti (NCI) continues by quoting from one of his own papers:

"An essential tool for the study of carcinogenesis, its modulation and its inhibition is the development of animal models for the experimental induction of cancers of the same types as those observed in human pathology. Particularly in the last decade, many new animal models have been developed, so that now we can say that most major forms of human cancers can be reproduced in animals by chemical induction.

They show histopathogenesis patterns very similar to those known from human pathology. This close correlation by itself strongly supports the evidence for a chemical origin of a large proportion of human cancers.

"The NCI laboratories, and those which have participated in the collaborative effort of the NCI Carcinogenesis Program, have contributed extensively to these advances. Recently developed models of chemically induced carcinogenesis include several examples of major epithelial cancers, such as lung cancer originating from the bronchial epithelium (Saffiotti *et al.* 1968, 1972a,b; Kaufman *et al.*, 1972a; Karbe and Park 1974); carcinoma of the larynx (Saffiotti and Kaufman 1975), large-bowel cancer (Druckrey, 1972; Ward *et al.* 1973; Weisburger 1973; Thurnherr *et al.* 1973; Ward 1974), carcinoma of the pancreas (Pour et al. 1974, 1975; Reddy and Rao 1975; Pledger *et al.* 1975; Levitt *et al.* 1977), kidney carcinoma (Reuber 1974a,b; Dees *et al.* 1976; Heatfield *et al.* 1976), urinary-bladder carcinoma (Saffiotti *et al.* 1967a; Tiltman and Friedell 1971; Hicks and Wakefield 1972; Hicks *et al.* 1975), and mammary carcinoma (Gullino *et al.* 1975)." (Saffiotti, 1977a, pp. 1317–1318)

Dr. David Baltimore (MIT) offered the following statement:

"There is every reason to believe that the gross principles of carcinogenesis as studied in animals are relevant to humans. Therefore, compounds that increase incidences of tumors in animals should have the same potential in humans. Human physiology clearly differs from animal physiology so a one-to-one mapping of events in animals onto humans should not be expected, but general principles should carry over." (Baltimore, S. 1–2)

Dr. Robert Squire (Johns Hopkins University) commented on the similarities between cancer in different species:

"Although the incidences vary with the species, virtually every type of cancer observed in man is also observed in some other animals and there is no reason to presume that the causative factors differ fundamentally between species. On the contrary, our knowledge of cancer mechanisms indicate that they apply to all mammals and perhaps all animals. At cellular and molecular levels, we are all quite similar." (Squire, S. 11)

Other witnesses who expressed general support for OSHA's proposed use of experimental animal evidence included: Dr. Curtis Harris (NCI), (Harris, Tr. 1954); Dr. Benjamin Trump (Univ. of Maryland), (Trump, Tr. 2016); Dr. Samuel Epstein (Univ. of Illinois, S. 30); Dr. Renate Kimbrough (Center for Disease Control), (Kimbrough, Tr. 1775; Dr. Richard Bates (NIEHS; FDA) S. 12; Dr. William Lijinsky (Frederick Cancer Research Center), S. 30; Dr. Paul Kotin (Johns-Manville), S. 20; Dr. William Butler (NACA), S. 11; Dr. Francis J. C. Roe (AIHC), S. 71; Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska), S. 14; Dr. Ronald Hart (Ohio State Univ.), S. 7–28; Dr. Richard Wilson (Harvard Univ.), S. 14; Dr. Perry Gehring (Dow Chemical Co.), Tr. 5172; Dr. David Hoel (NIEHS), Tr. 2187; and the Consumer Product Safety Commission, Exhibit 39, p. 25).

In addition to these general statements about the similarities between the effects of carcinogens in mammalian test animals and humans, some specific new evidence on the similarities at the cellular and molecular levels was also introduced. The review by Dr. Saffiotti (1977a), in which the development of a number of specific animal models of human cancers was summarized, has already been quoted above. Dr. Saffiotti concluded:

". . . many new animal models have been developed, so that now we can say that most major forms of human cancers can be reproduced in animals by chemical induction. They show histopathogenesis patterns very similar to those known from human pathology." (Saffiotti, S. 21)

Dr. Curtis Harris (NCI) and Dr. Benjamin Trump (Univ. of Maryland) introduced their work on the comparative metabolism and mechanisms of action of chemical carcinogens. In Dr. Harris's words:

"These findings indicate a remarkable qualitative similarity in the response of animal and human tissues to carcinogens." (Harris, S. 3)

Dr. Trump summarized his findings as follows:

"1. *There is an extremely close correspondence between certain types of human cancer and cancers induced in experimental animals by chemical carcinogens.* This correspondence has been demonstrated in our laboratory for lung cancer (in humans and hamsters) and kidney cancer (in humans and rats). The tumors in humans and animals appear virtually identical in histogenesis, ultrastructural morphology, and cytochemistry. Preliminary results indicate a similar correspondence for tumors in other tissues, including pancreas, breast, colon, bladder, cervix, prostate, and liver.

"2. Studies of the development of kidney carcinomas in rats show that *early lesions previously termed adenomas are transplantable and presumably represent adenocarcinomas in situ.*

"3. *Experimental exposure of human lung tissues* (maintained as xenografts in immune-deficient mice) *to carcinogens results in a sequential development of early lesions exactly resembling that seen in specimens from patients with lung cancer and in hamsters treated with BP–Fe_2O_3.*

"4. *Both human and animal tissues metabolize chemical carcinogens to mutagenic metabolites which bind to DNA.*

"5. There is great variability (up to 75-fold) between individuals in the ability of their tissues to bind mutagenic metabolites to DNA. *This variability appears to reflect inter-individual variability in susceptibility to chemical carcinogenesis.*

"In general, these results provide strong support for the use of experimental animal systems in identifying carcinogens which pose a risk to humans. In addition, tissue culture systems are proving to be excellent tools for the identification of carcinogens and mutagens, and for study of mechanisms of carcinogenesis." (Trump, S. 12–13, emphases in original)

Dr. Emmanuel Farber (Univ. of Toronto) presented a detailed account of his own work on the development of liver cancer in rodents in response to chemical carcinogens. He added the following conclusion emphasizing the direct relevance of this work to humans:

". . . there is an impressive basic similarity in etiology, pathogenesis and pathology between hepatocellular carcinomas in experimental animals and humans. In the animal, the role of cell damage and cell proliferation early in carcinogenesis is becoming evident. In the human, liver cancer is frequently associated with pre-existing liver cirrhosis and occurs in highest incidence in parts of the world in which liver damage by chemicals and viruses is most in evidence. The patterns of growth, morphology and life history of liver cancer in experimental animals and in humans are unusually alike. For these and other reasons stated in Appendix D, there is abundant evidence for the thesis that liver cancer development in experimental animals is a valid and reliable model for human liver cancer." (Farber, S. 4–5, citing Farber, 1978)

Other witnesses who testified to the similarity between humans and mammalian animals in metabolic, cellular and pathological aspects of carcinogenesis included: Dr. Elizabeth Weisburger (NCI), S. 3; Dr. Robert Squire (Johns Hopkins Univ.), S. 10–11; Dr. Arthur Upton (Director, NCI), S. 13; Dr. Harold Stewart (NCI), Exhibit B; Dr. Nathan Dubin (Medical College of Pennsylvania) S. 19–21; and Dr. Melvin Reuber (Frederick Cancer Research Center), S. 2. OSHA long ago accepted this principle. In the preamble to the standards for the 14 carcinogens, OSHA stated:

"A major question of occupational carcinogenesis relates to the extrapolation of results of animal experimentation to humans. The basis of numerous objections to the proposals is that, even assuming the validity of animal experiments, such do not furnish sufficient evidence that the substances involved are carcinogenic to humans. Extrapolation of results obtained by animal experimentation is alleged to be vitiated by several considerations: (a) That certain cancers are specific only to some species; (b) that the conditions of animal experiments are out of proportion to, and not consistent with conditions prevailing in industrial exposure; and (c) that no cancers have yet been detected in humans exposed to the

substances. For those substances whose metabolism is understood, and is similar in both animals and man, the fact that they induce cancers in animals warrants the expectation that they will induce cancers in men. This applies to the substances which cause urinary bladder cancers in animals acting, not directly, but indirectly through the mediation of metabolites formed both in experimental animals and in exposed workers. This is also true of those substances which apparently require no metabolic alteration but attack a particular biologic system (e.g., respiratory tract, alimentary canal) which is similar in both animals and humans.

"The objections raise the much broader issue of human exposure to a chemical which is only known to have caused cancers in experimental animals. It is important to note that some opponents of the regulation of such chemicals do not advocate treating them as if they were harmless with respect to carcinogenic potential. Several employers, for instance insist that such substances must be treated with "care" or "respect", while also insisting that they call for significantly less protection than those substances known to be human carcinogens.

"We think it improper to afford less protection to workers when exposed to substances found to be carcinogenic only in experimental animals. Once the carcinogenicity of a substance has been demonstrated in animal experiments, the practical regulatory alternatives are to consider them either non-carcinogenic or carcinogenic to humans, until evidence to the contrary is produced. The first alternative would logically require, not relaxed controls on exposure, but exclusion from regulation. The other alternative logically leads to the treatment of a substance as if it was known to be carcinogenic to man.

"We agree with the Director of NIOSH, and the report of the Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens to the Surgeon General, U.S. Public Health Service, April 22, 1970, that the second alternative is the responsible and correct one. This decision accords with the work practices of some who object to the proposed regulation." (39 FR 3756 at 3757–58)

This position was affirmed by the Third Circuit Court of Appeals which held in *Synthetic Organic Chemical Manufacturers' Association v. Brennan,* 503 F.2d 1155, 1160 (3d Cir. 1974) that: "there does exist substantial evidence in the record as a whole to support the Secretary's finding that [ethyleneimine] is carcinogenic in rats and mice and, in the absence of evidence of carcinogenicity in humans, the Secretary properly weighed the only available alternatives."

Other agencies and expert scientific committees have also agreed. In *In Re Shell supra,* the EPA Administrator stated:

"The ultimate issue in this suspension proceeding is whether Aldrin-Dieldrin is carcinogenic in man. Because man's response to carcinogens is similar to that of rodents, the finding that a substance is carcinogenic in experimental animals indicates that it poses a similar risk to man."

In affirming that decision, the Court of Appeals for the District of Columbia stated at 510 F.2d at 1299:

"The validity of extrapolation to humans from data derived from tests on animals is also a matter within the agency's expertise. There was testimony before the Administrator to support such extrapolation and this court has acknowledged the significance of test animal data when cancer is involved. Use of animal data is particularly appropriate where, as here, accurate epidemiological studies cannot be conducted because virtually universal contamination of humans by residues of aldrin/dieldrin make it impossible to establish an uncontaminated human control group. The long latency period of carcinogens further hinders epidemiological research, and the ethical problems of conducting cancer experiments on human beings are too obvious to require discussion. Although extrapolation of data from mice to men may be quantitatively imprecise, it is sufficient to establish a "substantial likelihood" that harm will result. Cf. Society of Plastics Industry, Inc. v. OSHA, 509 F2d. 1301, at 1308 (2d Cir. 1975)." (510 F2d at 1299)

And in proposing to ban the use of chloroform in drug and cosmetic products, FDA stated:

"Although he is not aware of any direct evidence that chloroform induces cancer in man, the Commissioner recognizes that the positive finding of cancer in test animals in the National Cancer Institute report indicates chloroform may pose a risk of cancer for humans. Experience has indicated that, with one or two possible exceptions, compounds that are carcinogenic in humans are also carcinogenic in one or more experimental animal bioassay systems. In addition, several compounds first detected as a carcinogen in experimental animals were later found to cause human cancer. The clear demonstration that a compound is carcinogenic in experimental animals must, therefore, be taken as evidence that it has a potential for carcinogenesis in humans unless there is strong evidence to the contrary." (41 FR 15027)

In finalizing that decision some two months later, FDA stated:

"The Commissioner considers the fact that a substance has been shown to be an animal carcinogen must be taken as evidence that it has a potential for carcinogenesis in humans unless there is strong evidence to the contrary." (41 FR 26844)

And, in banning "TRIS", the Consumer Product Safety Commission stated:

"The Commission has no conclusive data that establish that TRIS has caused cancer in humans. Since cancers develop over many years and cannot be easily linked to particular causes, this is not unexpected. The Commission's Office of the Medical Director (OMD) believes that once a substance is established as an animal carcinogen, it can never be assured as a safe substance for human exposure. In addition, OMD believes that all known human carcinogens have been shown to be carcinogenic in laboratory animals." (footnotes omitted). (42 FR 28061)

In "General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances", prepared for NCI by the Subcommittee on Environmental Carcinogenesis of its National Cancer Advisory Board (NCAB), (February, 1977), it was stated that studies with expermental animals represent "a major source of data on carcinogenicity". Although present knowledge is not sufficently advanced to allow a precise determination of whether a carcinogen identified solely by means of a bioassay in animals will or will not be carcinogenic in humans, and because it is not ethically nor practically feasible to undertake to study the effects on humans of substances identified as carcinogens through animal studies, it is necessary to rely on the correlation between substances studied in animals and those known to induce cancer in humans. The NCAB Report stated that:

"[e]xperience has indicated that, with one or two possible exceptions, compounds that are carcinogenic in humans are also carcinogenic in one or more experimental animal bioassay systems. In addition, several compounds first detected as carcinogens in experimental animals were later found to cause human cancer. Demonstration that a compound is carcinogenic in animals should therefore, be considered evidence that it is likely to be carcinogenic in humans, unless there is strong evidence in humans to the contrary." (NCAB Report, 1977, p. 461; Exhibit B to Weinstein Statement)

The validity of using animal data as a qualitative indication of potential human effects has long been recognized by scientific advisory committees, and other governmental bodies in addition to the testimony of the witnesses cited above and below; portions of the extensive discussion by expert committees of the general criteria and principles applied to the design and interpretation of studies in animals will be traced to illustrate the varying conditions accepted for testing for carcinogenicity in animals (including length of the exposure period, number of animals to be employed, kinds of controls to be used, etc.) and the necessity for reliance on such data despite some uncertainties that might arise. As far back as 1959, a report of the National Research Council's Food Protection Committee provided one of the earliest reviews of the problems of identifying carcinogens. In the case of

food additives, it was noted that epidemiological studies were even more difficult to conduct in the general population than for occupational exposures, and a series of general considerations and principles underlying evaluations of carcinogenicity from animal studies was outlined. The report stated with regard to substances studied by administration to experimental animals that:

"[t]here is general agreement as to the carcinogenicity of these substances and, although the carcinogenicity of all of them for man has not been demonstrated, it is unlikely that anyone would defend the addition of any of them to the human diet". (NRC, 1959, p. 6)

In 1961, a joint committee of the Food and Agricultural Organization (FAO) and the World Health Organization (WHO) issued a report entitled: "Evaluation of the Carcinogenic Hazards of Food Additives" (WHO Tech. Rept. 220). The Committee, in its report, noted the ". . . difficulty of carrying out and interpreting epidemiological studies" and recognized that tests in animals are necessary to identify carcinogens. The Committee stated that:

". . . tests on experimental animals cannot provide irrefutable proof of the safety or carcinogenicity of a substance for the human species. However, it is at least reassuring that the known carcinogenic activities of certain chemicals in man are similar in many ways to those found in experimental animals." (WHO Tech. Rept. 220, 1961, p. 6)

As a minimum safeguard, the committee said an ". . . investigation of the tumor incidence in a chronic toxicity test . . ." should be performed, which ". . . should involve the study of an adequate number of animals of two species (*e.g.*, rats and mice) and subjected to the feeding of a suitable dose range of the substance under question for the lifetime of the animals." (*Ibid.*, p. 7)

The Committee also noted its view of the need to use sensitive animals and stated:

"Both sexes of each of at least two species of animals should be used in the tests throughout their lifespan. In most cases these species would be rats and mice. Hamsters or dogs might be suitable, but guinea-pigs, for example, appear to be resistant to some known carcinogens. The use of dogs in carcinogenicity tests has disadvantages. Because of the expense of maintenance, it is difficult to use a sufficient number to detect a low incidence of cancer, and the life span of the animal is 12–15 years." (*Ibid.*, p. 8)

The Committee report further stated that to establish valid negative results requires either the "unrealistic" use of large numbers of animals or dose levels ". . . far in excess of those recommended for human consumption." (*Ibid.*, p. 9). Thus, to reduce the possibility that studies in animals will be too insensitive to detect the carcinogenic action of a substance, the Committee pointed out that large doses of the substance are administered to the animals, despite the fact that in some cases large doses of many substances may cause nonlethal, non-carcinogenic but toxic effects in animals.

A report published in 1969 by the International Union Against Cancer (UICC, 1969) discussed the results of a study of:

". . . those aspects of experimental carcinogenesis in animals which have a direct bearing on the problems of environmental cancer in man . . .", with particular emphasis on: ". . . methods of testing substances suspected of being carcinogenic in man, and to problems related to testing procedures." (UICC, 1969, p. 1)

The report states:

"The need to formulate minimal requirements for satisfactory testing of substances suspected of being carcinogenic for man has been recognized for a long time, and a number of international and regional bodies had already discussed it in some detail and published specific recommendations . . . These earlier recommendations differed one from another in several respects, due in part to conflicting views among the various experts in the field, though some of the divergencies of opinion were more concerned with differences between minimal and optimal requirements." (*Ibid.*, p. 11)

The report then discussed some of the procedures generally employed in animal bioassays for carcinogenicity, the presentation of data, their interpretation, and other points, including priorities for testing. In the report it was also stated that positive findings should outweigh negative results:

"It is generally recognized that negative results of biological testing are less significant than positive results, in relation to human application. This is all the more true when testing procedures are inadequate." (*Ibid.*, p. 18)

In the United States, a review of concepts to be applied in carcinogenicity testing was also published in 1969 by the Commission on Pesticides and Their Relationship to Environmental Health, appointed by the Secretary of the Department of Health, Education and Welfare (Mrak Commission). The Technical Panel on Carcinogenicity recommended that food additives and contaminants be tested for possible carcinogenic effects by means of adequate long-term bioassays:

"The minimum requirements for such bioassays should include: Adequate numbers of animals of at least two species and both sexes with adequate positive and negative controls, subjected for their lifetime to the feeding of a suitable dose range of the test material, including doses considerably higher than would be present in food . . . any substance which is shown conclusively to cause cancers in animals when tested under these conditions should be considered potentially carcinogenic for man . . . " (Mrak Commission, 1969, p. 467)

* * * * *

" . . . the number of animals in each test group should be sufficient throughout the tests to yield statistically significant results. It is important to stress that the detection of positive results in these bioassays depends on the development of tumor incidences significantly above the threshold of detectability for a given number of animals. Any carcinogenic effect below these levels will not be detected by the bioassays used." (*Ibid.*, p. 465)

* * * * *

"The species most practical for testing are rats, mice, and—as more recently shown—hamsters. Strains and colonies should be selected to provide adequate sensitivity to tumor induction, as revealed by positive control tests with known carcinogens." (*Ibid.*, p. 465)

The Technical Panel noted (footnote 2 on p. 465) that:

"[t]he use of nonrodent species, recommended in the earlier reports, has now been substantially dropped. A suitable, practical nonrodent species would be useful but it is not available at this time . . . . While dogs have been employed for tests of carcinogenicity, with noteworthy success in selected cases (bladder carcinogenicity of aromatic amines), the requirement of lifetime feeding makes this species too expensive, in terms of time and funds, to be employed routinely." (*Ibid.*, p. 465)

The Technical Panel also noted the:

"(g)eneral principles and criteria for evaluation of carcinogenic hazards . . . laid down by several expert committees conceived in the last fifteen years by scientific and public health agencies . . ." (*Ibid.*, p. 464)

and stated that:

"Recommendations made in these reports express a remarkably unanimous view on the general principles and criteria to be followed for carcinogenesis safety evaluations, widely accepted in principle by the scientific community (references omitted)." (*Ibid.*, p. 464)

In the report, the Technical Panel discussed the uncertainties as to the relevance and extrapolation of animal data to humans, stating that such uncertainties:

". . . are a cause for concern and caution in interpretation of results. It should be noted, however, that a remarkable degree of concurrence has been found to exist between chemical carcinogenesis in animals and that in man where it has been studied closely." (*Ibid.*, p. 482)

Thus, in recommending that human exposure to those pesticides considered to present a potential health hazard to humans should be reduced, the Mrak Commission cautioned that:

". . . It is of utmost importance that the results of screening tests be scientifically and rationally considered. The correct interpretation of hazards to human health is sometimes extraordinarily difficult. It must involve the transfer of the results of animal experiments to prediction of human effects. In addition, the screening process frequently involves preliminary examination of the effects of massive dosages, possible contamination of test samples, and other factors which affect proper interpretation . . . (but) . . . (t)he health and welfare of the public must be effectively protected." (*Ibid.*, p. 10)

Also in 1969, a Panel on Carcinogenesis of FDA's Advisory Committee on Protocols for Safety Evaluation prepared a report (FDA Panel Report) and later published it ("Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides." *Toxicol. Appl. Pharmacol.*, 20, 419 (1971)). The FDA Panel concerned itself ". . . with an evaluation of the present status of testing for carcinogenic action of food additives and other chemicals, which come into contact with man principally through his diet . . . and . . . consideration of recommended test procedures for carcinogenesis" (p. 425). A number of issues involved in the reliance on tests in animals under controlled conditions were discussed. Of the species of animals that might be used, the Panel said:

"There is general recognition that new species in addition to the commonly used rodents are needed for carcinogenicity testing. Increasing the number of species used would greatly increase the margin of confidence with which safety can be predicted . . . The most discussed additional species are primates. Recent studies show certain primates to be highly susceptible to some carcinogens; however, much more work is needed to justify the additional expense and time that would be necessitated by the introduction of these animals in routine test procedures." (*Ibid.*, p. 426)

And in a discussion of the use of dogs, the Panel said:

"There is general agreement that the dog is not a practical test animal because of its size and relatively long life span." (*Ibid.*, p. 426)

The FDA Panel also delineated the responses in experimental animals as compared with a series of untreated (control) animals that ". . . may suggest the presence of a carcinogenic hazard . . ." They are:

". . . (1) an increased incidence of tumors of a type seen commonly in the control animals, (2) an occurrence of a type of tumor not seen at all in the control animals or (3) a combination of the occurrence of a different type of tumor and an increased incidence of one or several types of tumors seen in the controls. In some experiments the only manifestation of an effect consists of (4) an earlier occurrence of tumors in the treated animals than in the controls, the incidence being the same in both. In yet another variation the only effect seen may consist of (5) an increase in the number of tumors per animal, the number of tumor bearing animals being the same." (*Ibid.*, pp. 419–420)

In 1969, the NRC Food Protection Committee prepared another report, "Evaluating the Safety of Food Chemicals," which was published in 1970 (NRC, 1970). The Committee noted that the previous reports of the Food Protection Committee, the Joint FAO/WHO Expert Committee, and the FDA contained:

". . . complementary statements of the principles underlying evaluation of the safety of food chemicals and . . . set forth proposed procedures for accomplishing the evaluation . . ." (NRC, 1970, p. 1)

The Committee stated that it was:

". . . not the purpose of this report to present another set of principles and procedures, but rather to review the purposes and value of what have become conventional procedures . . ." (*Ibid.*, p. 1)

The Committee discussed difficulty in carrying out controlled epidemiological studies and stated that:

"(c)ontrolled experimental studies in man, though desirable, have limited predictive value . . ." (*Ibid.*, p. 44)

and therefore:

"(i)t is clear that appropriate and well-executed animal studies are more likely to provide a substantial background of biological data from which to judge safety than are studies in man alone." (*Ibid.*, p. 45)

In a discussion of the evaluation of the carcinogenic hazards of chemicals for man, the Committee stated that:

"(o)n both ethical and practical grounds, the possible carcinogenic effects of chemicals to which man might be exposed must be determined in experimental animals, generally in short-lived species. The extrapolation of the results of these determinations to man rests on two basic findings:

"1. Despite a great variety of studies, no significant aspect of the natural occurrence, induction, and properties of cancer has been shown to differ fundamentally between man and experimental animals.

"2. Considerable assurance of the general applicability of the tests can be derived from the fact that the chemicals generally known to be carcinogenic in man also induce neoplasia (tumors) in experimental animals.

"(M)any clear differences in the activities of chemical carcinogens in various species exist, however, and the unpredictable nature of species differences is the principal limitation to the extrapolation of results from studies with experimental animals to man." (*Ibid.*, p. 47)

In 1970, the report, prepared for the Surgeon General by the Ad Hoc Committee of NCI, dealt with problems of exposure to chemical agents from all sources and ". . . the scientific criteria for evaluation of carcinogenic hazards." (NCI, 1970, p. 1). In emphasizing the broader scope of their report, the Committee said:

"(M)any previous recommendations on the criteria to be used for evaluating environmental chemical carcinogenic hazards have been made for specific sources of exposure or for specific groups of substances (e.g. food additives, pesticides, certain occupational carcinogens). In some cases this approach has led to an uneven assessment of risks from different sources and to an uneven approach to preventive measures." (*Ibid.*, p. 1)

The Committee acknowledged that:

"(t)he present state of the art requires long-term bioassays in mammalian species for the experimental identification of carcinogenic activity . . . A body of knowledge has developed over the years on the response of experimental animals to chemical carcinogens. Several committees of experts in the field of carcinogenesis convened by national and international bodies over the past 15 years have formulated general principles for performance and evaluation of carcinogenesis studies in animals. The recommendations put forth by these committees have shown remarkable unanimity (specifically cited were WHO Tech Repts 276 and 220, FDA Panel Report, Mrak Commission Report) and are widely accepted in principle by the scientific community" (*Ibid.*, p. 6)*

Among the Committee's recommendations were:

"Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard for man. Exceptions should be considered only where the carcinogenic effect is clearly shown to result from physical, rather than chemical, induction, or where the route of administration is shown to be grossly inappropriate in terms of conceivable human exposure.

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*The committee cited the following references: P. Shubik and J. Sice, "Chemical carcinogenesis as a chronic toxicity test: A Review," *Cancer Res. 16.* 728–742 (1956). D. B. Clayson, "Chemical Carcinogenesis," Boston, Massachusetts, Little Brown and Co., 1962. W. C. Hueper, W. D. Conway, "Chemical Carcinogenesis and Cancers," Springfield, Illinois, C. C. Thomas 1964. J. H. Weisburger and E. K. Weisburger, "Tests for Chemical Carcinogens," *In* Methods in Cancer Research, Volume I. (H. Busch, ed.), New York, New York, Academic Press Inc., 1967, pp. 307–387. J. G. Arcos, M. G. Argus, G. Wolf, "Testing Procedures," In "Chemical Induction of Cancer," Volume I (J. G. Arcos, M. G. Argus, and G. Wolf, eds.), New York, New York, Academic Press Inc., 1968, pp. 340–463.

". . . Data on carcinogenic effects in man are only acceptable when they represent critically evaluated results of adequately conducted epidemiological studies.

". . . Evidence of negative results, under the conditions of the test used, should be considered superseded by positive findings in other tests. Evidence of positive results should remain definitive, unless and until new evidence conclusively proves that the prior results were not causally related to the exposure.

. . . A basic distinction should be made between intentional and unintentional exposures.

. . . No substance developed primarily for uses involving exposure to man should be allowed for widespread human intake without having been properly tested for carcinogenicity and found negative.

". . . Any substance developed for use not primarily involving exposure in man but nevertheless resulting in such exposure, if found to be carcinogenic, should be either prevented from entering the environment or, if it already exists in the environment, progressively eliminated." (*Ibid.*, pp. 1, 2)

The Committee also stated:

"Any substance which is shown conclusively to produce tumors in animals . . . should be considered potentially carcinogenic for man." (*Ibid.*, p. 7)

More recent reports further confirm the widely recognized validity of animal experiments for establishing the carcinogenic potential of substances. An ongoing series of monographs published by the International Agency for Research on Cancer of WHO (IARC), beginning in 1972, lists animal data and any epidemiological evidence of cancer in humans when discussing the carcinogenic potential of individual substances or of classes of substances. The monographs were initiated as a result of a recommendation in 1970 of the IARC Advisory Committee on Environmental Carcinogenesis:

". . . that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented." (IARC, 1972, Vol. 1, p. 8)

The stated objective of the monographs is:

". . . to achieve a balanced evaluation of data through the deliberations of an international group of experts in chemical carcinogenesis and to put into perspective the present state of knowledge with the final aim of evaluating the data in terms of possible human risk, as well as to indicate the need of research efforts." (IARC, 1972, Vol. 1, p. 8)

The monographs emphasized that the response to a carcinogen in animals may be observed in several forms:

"(*a*) as a significant increase in the frequency of one or several types of neoplasm, as compared with other than zero frequency in control animals;

"(*b*) as the occurrence of neoplasms not observed in control animals;

"(*c*) as a decreased latent period as compared with control animals;

"(*d*) as a combination of (*a*) and (*c*)." (IARC, 1972, Vol. 1, p. 10)

In 1975, the National Research Council published two reports that addressed the question of carcinogenicity testing in animals. In a report on present and alternative technologies for pest control (NRC Pest Control), it was concluded:

". . . the carcinogenic risks, and other health hazards, of pesticides require continuing evaluation by testing with laboratory mammals; and that despite the problems involved in translating the results from such experiments to human risk, the present techniques are sufficiently reliable to justify registration actions based upon such data alone, or an interim basis, until evidence convincingly demonstrates that there is no human risk." (NAS, 1975a, p. 5; Hearing Exhibit 2)

In a report on principles for evaluating chemicals in the environment (NRC Principles for Evaluating Chemicals), a section was devoted to chemical carcinogenesis which discussed aspects of experimental design for carcinogenicity testing.

The report stated:

"[r]odents are the animals of choice for carcinogenesis tests because of their convenience, comparatively short life span and proven susceptibility to a broad range of carcinogenic agents." (NAS, Evaluating Chemicals, 1975b, p. 150)

In 1976 the Subcommittee on Environmental Carcinogenesis of the National Cancer Advisory Board, National Cancer Institute, issued a report entitled "General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances" (NCAB report), June 2, 1976. The report stated:

". . . Demonstration that a compound is carcinogenic in animals should, therefore, be considered evidence that it is likely to be carcinogenic in humans, unless there is strong evidence in humans to the contrary." (NCAB Report, 1977, p. 461; Exhibit B to Weinstein Statement)

A number of expert review committees which have reported since 1976 on various aspects of the identification of carcinogens have expressed general support for the use of animal testing. The Safe Drinking Water Committee of the National Academy of Sciences made the following summary statement:

"EFFECTS IN ANIMALS, PROPERLY QUALIFIED, ARE APPLICABLE TO MAN

"This premise underlies all of experimental biology and medicine, but because it is continually questioned with regard to human cancer, it is desirable to point out that cancer in men and animals is strikingly similar. Virtually every form of human cancer has an experimental counterpart, and every form of multicellular organism is subject to cancer, including insects, fish, and plants. Although there are differences in susceptibility between different animal species, between different strains of the same species, and between individuals of the same strain, carcinogenic chemicals will affect most test species; and there are large bodies of experimental data that indicate that exposures that are carcinogenic to animals are likely to be carcinogenic to man, and vice versa.

"Evidence that circumstances leading to cancer induction in humans are also applicable to experimental animals stems from the very first observation of chemical carcinogenesis—the appearance of cancer of the scrotum in chimney sweeps, observed by the British surgeon, Percival Pott, in 1775. It was not until modern times that a substance implicated in human cancer was found to be carcinogenic in animals, when the Japanese scientists, K. Yamagiwa and K. Ichikawa, found in 1915 that extracts from coal tar caused cancer when applied to the skin of experimental animals. Many pure carcinogenic chemicals have since been isolated from a wide variety of "tars" derived from incomplete combustion of organic matter, such as coal, wood, and tobacco. There is little doubt that these and other chemicals, alone or in combination, are responsible for the greatly increased incidence of lung cancer among smokers. With the possible exception of arsenic and benzene, all known carcinogens in man are also carcinogenic in some species, although not in all that have been tested." (NAS, 1977a, pp. 53–54; Appendix I to Rall Statement)

The final OTA report, *Cancer Testing Technology and Saccharin* stated:

"Animal tests are accepted as valid, reliable predictors that a substance will produce cancer in humans." (OTA, 1977, p. 5; Exhibit C to Weinstein Statement)

The report continued:

"Animal tests are the best current methods for predicting the carcinogenic effect of substances in humans. All substances demonstrated to be carcinogenic in animals are regarded as potential human carcinogens; no clear distinctions exist between those that cause cancer in laboratory animals and those that cause it in humans. The empirical evidence overwhelmingly supports this hypothesis." (*Ibid.*, p. 11)

In the latest volume of the IARC Monograph series, the preamble states:

"For many of the chemicals evaluated in the first 17 volumes of the *IARC Monographs* for which there is *sufficient evidence* of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable to regard for practical purposes such chemicals as if they were carcinogenic to humans." (IARC 1978, Vol. 17, p. 20)

The National Academy of Sciences Committee for a Study of Saccharin and Food Safety Policy reported as follows:

"Since animal studies that are properly conducted to detect carcinogenic activity are qualitatively predictive of human responses, the committee concludes that saccharin ingestion presents a predicted cancer risk to humans. However, because of the substantial uncertainties in extrapolating from experimental doses to human exposure levels, the committee concludes that quantitation of risks to humans cannot be made with confidence." (NAS, 1978, p. T–3, emphasis in original)

In addition, a report by the Food Safety Council made extensive recommendations for the use of animal tests in the evaluation of chronic hazards of food components, including carcinogenicity:

"The selection of test species for chronic testing is limited by many practical considerations and has been considered in detail in the references cited above. Since it is generally acknowledged that the test period should encompass a major portion of the lifespan of the test species, the selection is limited to those mammalian species with relatively short longevity. It is also necessary that there exist adequate biological knowledge of the species, including information on required husbandry practices and spontaneous diseases and their management. Laboratory animals such as dogs, and non-human primates, although perhaps desirable in many respects, are usually unacceptable because of their relatively long lifespans. There may be an instance, however, in which the nature of the toxicity or the procedures required will necessitate the use of larger species such as dogs, cats or non-human primates."

"Among laboratory rodents, mice and rats have been the traditional test species employed in chronic testing. Their lifespan, size and cost are well suited to this purpose. Further, there is extensive experience and information of the biological characteristics, husbandry and diseases of mice and rats, exceeding that of any other animals except domestic veterinary species. It is, therefore, recognized that mice and rats remain the species of choice under most circumstances unless specific considerations dictate otherwise. Experience with Syrian hamsters is expanding and this species is also considered acceptable for chronic toxicity testing. However, there is not yet sufficient biological data to consider hamsters as replacements for rats or mice, but rather as an acceptable third species. (Food Safety Council, 1978, pp. 97–98; Hearing Exhibit 227)

C. OSHA's General Conclusions

The validity of qualitatively extrapolating animal test results to humans is firmly based upon substantial and empirical evidence in the Record, as we pointed out above. Not only have experiments in test mammalian animals given positive carcinogenic test results for every compound known to cause cancer in humans, except arsenic and perhaps benzene, but although there may be wide variations in the susceptibility of various species to cancer, evidence indicates that a substance that causes cancer in one mammalian animal species is likely to do so in most other mammalian species tested. Substantial evidence and scientific data in the Record indicate, in sum, that laboratory animals are suitable test models for determining the cancer-causing potential of a toxic substance to humans.

OSHA concludes that the general principle that substances shown to be carcinogenic in test animals should be presumed to pose a qualitative carcinogenic hazard to exposed humans was overwhelmingly supported, except as so qualified below; indeed, the specific scientific documentation for the principle is steadily being enlarged. It is for these reasons that the relevant portion of the OSHA Cancer policy states at 1990.143(b):

(b) *Positive animal studies.* Positive results obtained in one or more experimental studies conducted in one or more mammalian species will be used to establish the qualititative inference of carcinogenic hazard to workers. Arguments that positive results obtained in mammalian species should not be relied upon will be considered only if evidence is presented which meets the criteria for consideration specified in § 1990.144(c) or § 1990.144(f).

Although a large number of witnesses testified about the way in which animal data should be used in identifying, classifying, and regulating potential occupational carcinogens, almost all the witnesses and participants accepted the general proposition that a substance found to be carcinogenic in animals should be regarded as a potential human carcinogen. This virtually unanimous view is illustrated by the above discussion and analysis. There was however, concern expressed about how OSHA's general policy will in fact be applied in regulatory activity in the future. In the preamble to the proposed regulation, most of the specific concerns discussed by the participants in this rulemaking were raised and discussed under the following 10 titles:

1. Mammalian Species.
2. Positive versus Non-positive Results.
3. Testing at High Doses.
4. Species or Organ Specificity.
5. Statistical Significance.
6. How much weight should be placed upon the incidence of benign tumors in animals as an indication of potential carcinogenic hazard in man?
7. How much weight should be placed on the induction of a type of tumor which occurs spontaneously in untreated animals?
8. Which routes of exposure of experimental animals are to be considered appropriate for extrapolation to man?
9. How much confirmation of positive results is necessary?
10. Can "safe" or "no effect" levels be set for exposure to chemical carcinogens?

The evidence presented in this Record on these points will therefore be discused below under the same 10 titles. In addition, concern was expressed on additional points which were raised elsewhere in the proposal, were fully aired during the rulemaking and are discussed below as follows:

11. Criteria for Assessing Animal Studies.
12. Promoters.
13. Metabolism.

The evidence presented in the Record on these points and the other general issues raised will also be discussed below.

D. THE SPECIFIC ISSUES

1. Mammalian Species

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA proposed that tests in any mammalian species would be regarded as appropriate for the prediction of potential hazard to exposed humans, whereas tests on non-mammalian species would not. OSHA specified that rats, mice and other mammalian species are the species of choice in carcinogenicity testing, and that positive results in any of these species would be given importance, *viz:*

"Mammalian species are those species of test animals generally considered directly relevant to man insofar as carcinogenicity testing is concerned. Other species, such as reptiles, have not been shown to have any such similarity to humans, insofar as carcinogenicity is concerned. Thus, OSHA relies, in general, only upon results found in testing of mammalian species. In that regard, the rat and mouse (and to a lesser extent the hamster) have traditionally been the species of choice for carcinogenicity testing, other mammalian species being useful for certain purposes but generally impractical for use in full-scale bioassays (WHO Tech. Rept. 220, p. 8; Mrak Commission, p. 465; FDA Panel Report, p. 426; NRC Principles for Evaluating Chemicals, p. 150). The choice of the rat and mouse is not only dictated by considerations of convenience, but because of their known susceptibility to agents known to be carcinogenic in humans as well as the similarity in the mechanisms of tumor induction (NRC, 1970, p. 47)." (42 FR 54160)

b. The Public's Response

(1) *General Support for the Proposed Position.*

Most witnesses and participants in this rulemaking expressed general support for OSHA's proposed position

that a positive result in any mammalian species is important and meaningful in the qualitative identification of a potential human hazard. Dr. Arthur Upton (Director, NCI) and Dr. Richard Griesemer (NCI) described the NCI Bioassay Program, the largest screening program under way for the identification of carcinogens, which uses rats and mice as the species of choice. In fact, NCI defines a chemical carcinogen as:

"... a chemical that has been demonstrated to cause tumors in mammalian species by induction of a tumor type not usually observed; or by induction of an increased incidence of a tumor type normally seen, or by its appearance at a time earlier than would be otherwise expected." (Sontag *et al.*, 1976, pp. 46–47; Appendix to Griesemer Statement)

Dr. Upton (Director, NCI) after discussing in general the lack of knowledge of the mechanisms of carcinogenesis commented:

"Given this lack of knowledge concerning mechanisms, I believe that a reproducible carcinogenic response in *any* species of test animal must be considered sufficient to describe the test compound as a carcinogen and so a potential threat to human health. I consider that a similar reaction in a second mammalian species is a confirmation of the carcinogenicity of the test agent, but it is not necessary before a finding of carcinogenicity and potential threat to human health can be made; negative results in a second or even third species of test animal do not in my mind establish that the test agent is not a potential threat for human beings. Given the variation in human susceptibility to carcinogens, I believe it unreasonable to ignore a finding of carcinogenicity in any mammalian test species when considering possible effects on human health. (Upton, S. 17)

Dr. David Baltimore (MIT) stated that:

"There is every reason to believe that the gross principles of carcinogenesis as studied in animals are relevant to humans. Therefore, compounds that increase incidences of tumors in animals should have the same potential in humans. Human physiology clearly differs from animal physiology so a one-to-one mapping of events in animals onto humans should not be expected, but generally principles should carry over." (Baltimore, S. 1–2)

Dr. Renate Kimbrough (CDC), in response to questioning, stated:

"It does not matter what species are we talking about. Whatever species you have a positive result in, that should be a signal saying that this compound is carcinogenic, and that the exposure to this compound ought to be reduced." (Kimbrough, Tr. 1777)

Dr. Richard Griesemer (NCI) also commented:

"We are certain today—and I used that advisedly—we are certain that there are no species differences amongst mammals for carcinogens, and that animal carcinogens are very likely if not certainly human carcinogens." (Griesemer, Tr. 957)

Dr. Matthew Meselson (Harvard Univ.) commented:

"... I would be very suspicious of any such claim of a species difference; not that there are not such claims, but that sometimes they have been based on inadequate information and they seem to live on like legends and not really be true." (Meselson, Tr. 1538)

Later, he summarized by saying:

"So, my impression on looking through the literature for the compounds I did is that you can get an exaggerated view of the importance of these species differences partly because of inadequate experimentation, partly because even when they do exist you have to ask how big are the differences in comparison with our purposes in getting a scale that covers the whole range of a million." (Meselson, Tr. 1541)

Dr. Melvin Reuber (NCI–FCRC) commented on the significance of the laboratory carcinogenicity findings to human health:

"Qualitatively, it has been shown that the formation and occurrence of tumors in man and other mammals—such as hamsters, mice and rats—is quite similar. In tests undertaken to date, it has been demonstrated, with two possible exceptions (arsenic and benzene), that every chemical which has been found to be carcinogenic in man is also carcinogenic in one or more mammalian test animals. Furthermore, the majority of chemical carcinogens which have undergone sufficient testing have been shown not to be species specific. That is, testing has shown that if these compounds will produce tumors in one species, it will very likely produce tumors in more than one, thus adding weight to any finding of carcinogenicity in tests using any mammalian species. Sufficient documentation is available on qualitative extrapolation of animal data that one must conclude that a finding of carcinogenicity in one mammalian species should be deemed to have relevance for other mammalian species—including man." (Reuber, 1977, pp. 14–15; Appendix C to Reuber Statement)

Dr. Bo Holmberg (Swedish NBOSH) raised the point that the insensitivity of epidemiological studies does not preclude action on results in mammalian species:

"The apparent low number of established occupational carcinogens is not a true indicator of the problem and certainly does not justify a lack of action on all chemical compounds inducing cancer in mammalian species." (Holmberg, S. 7)

Dr. Donald Millar (Acting Director, NIOSH) after a discussion of known human carcinogens commented:

"Of the human carcinogens mentioned above, almost all have been shown to be positive in rats and several of them are positive in mice. Fortunately, these are the mammalian species which are least costly to process, and, therefore, their use can be recommended with very few or no qualifications." (NIOSH, Appendix C, p. 2)

In a recently published set of recommendations, the Food Safety Council adopted a similar viewpoint:

"Among laboratory rodents, mice and rats have been the traditional test species employed in chronic testing. Their lifespan, size and cost are well suited to this purpose. Further, there is extensive experience and information of the biological characteristics, husbandry and diseases of mice and rats, exceeding that of any other animals except domestic veterinary species. It is, therefore, recognized that mice and rats remain the species of choice under most circumstances unless specific considerations dictate otherwise. Experience with Syrian hamsters is expanding and this species is also considered acceptable for chronic toxicity testing. However, there is not yet sufficient biological data to consider hamsters as replacements for rats or mice, but rather as an acceptable third species." (Food Safety Council, 1978, pp. 97–98; Hearing Exhibit 227)

A similar position was taken by the Consumer Product Safety Commission:

"(A) *Mammalian species.* CPSC generally will rely only upon results found in testing mammalian species as opposed to reptiles, fish, etc. As a practical matter, small mammals such as hamsters, rats and mice will be the test animals of choice, because of their convenience, relatively low cost, and susceptibility to agents known to be carcinogenic to humans." (CPSC, Hearing Exhibit 39)

(2) *Issues Raised at the Hearing.*

Despite the general consensus that mammalian species are generally appropriate for carcinogenicity testing, and that rats and mice are the species of choice, a number of witnesses objected to the use of certain mammalian test systems. In particular, objections were raised to the use of certain strains with high spontaneous incidence of tumors, and to the use of certain strains of mice. For example, the Food Safety Council continued as follows after the passage quoted above:

"There is controversy over the use of mice in toxicity testing, particularly with respect to the assessment of potential carcinogenic risk (Grasso, Crampton, and Hooson, 1977). The relevance of test results in mice is questioned primarily because of the high spontaneous rates of certain tumor types, and the effects of many modifying factors such as diet, viruses and hormones on the incidences. Particular concern is given to lymphomas, lung, liver and mammary tumors. It is true that certain strains of mice have high natural incidences of one or more of these tumors, and that their unusual genetic susceptibility may not be relevant to the human population. The use of such strains is appropriate for carcinogenesis research but not safety testing. However, several strains of mice have relatively low to moderate rates of spontaneous neoplasms and these are well

suited to carcinogenicity testing. The fact that environmental factors may modify the tumor rates in test animals does not invalidate animal experiments unless species specific responses can be demonstrated, because similar factors undoubtedly also influence human response to carcinogens. The important point is that genetic and environmental influences be uniform among treated and control animals. It is also argued that mice are excessively sensitive to carcinogens, but one may equally argue that their sensitivity is an advantage in safety testing and in the extrapolation of animal data to the genetically diverse human population." (Food Safety Council, 1978, p. 98; Hearing Exhibit 227)

A number of witnesses at the hearing presented specific testimony on these issues. For example, Dr. Robert Olson (St. Louis Univ.) summarized his discussion on the use of the mouse in extrapolating to humans:

". . ., it is very difficult to extrapolate carcinogenicity testing from mice to human beings because of the mouse's high basal tumor incidence, inconstant basal development of tumors over various periods of time, marked effects of diet and nutritional status, response to trace carcinogens in animal foodstuffs, hypersensitivity to endocrine and social factors, inconstant life span and changing age-dependent tumor incidence, sensitivity to infection by oncogenic viruses and metabolic pathways which do not parallel those in man. The Panel on Carcinogenicity of the Cancer Research Commission of the International Union against Cancer recommended strongly against the use of only one species in carcinogenicity testing. They said, 'To allow for differences in the pattern of response between man and animals, the testing of a suspected substance must be carried out in more than one species of animal. Ideally, the more species used, the better; in practice, some compromise must be reached' (84). For all these reasons, it is my view that using the mouse as the *sole* test animal in determining the potential human carcinogenicity of given compounds is not a sound biological approach." (Olson, S. 25, emphasis in original)

Drs. Paul Newberne and Adrianne Rogers (MIT) commented:

"The foregoing discussion of the significant incidence of liver nodules in a majority of mouse strains and substrains and the problems of classifying them leads one to conclude that the mouse leaves much to be desired as a species for safety testing. The results of studies upon which this report is based do not always give a clear indication of carcinogenic activity for a given chemical. The relatively rare mention of metastases or of histological features of hepatic tumors reported leads one to suspect that carcinogenic activity was, in some instances, based on the induction of nodules which may have been benign.

"In our opinion, with the foregoing documented information in mind, it is scientifically unsound to base any judgment as to chemical safety on mouse liver tumors alone until we understand the biological behavior of such lesions. (Newberne and Rogers, S. 16–17)

Dr. Paul Grasso (AIHC) stated:

"In the mouse, lymphomas, pulmonary adenomas, hepatomas and mammary tumours are found much more frequently than other tumours, and are readily induced by a number of chemical agents. As discussed in our publication entitled "The Mouse and Carcinogenicity Testing" (Ref. 9) important biological factors unrelated to treatment appear to play a major role in the development of these tumours so that even if there is a statistically significant difference between test and control, one cannot accept this as valid evidence of carcinogenic activity. Some of the factors responsible for the development of these four types of tumours are outlined in the following sections. (Grasso, S. 5)

His colleague Dr. Reginald Crampton (AIHC) also commented:

"From the cancer point of view there is no such animal as the mouse. For example, the male mice of strain C3H will spontaneously develop up to 85% incidence of liver tumours (8,9) whereas mice of strain SWR/J have a near zero incidence of liver tumours (10). There are many similar examples involving other types of tumours. Furthermore, there is evidence that within a single strain of mice the incidence of spontaneous tumours may change with time (11, 12)."

* * * * *

"Whilst the precise way in which cancer is caused in any species is unknown, several predominant factors are known to affect its appearance in the mouse, which are absent or which appear to play a minor role in other species, including man. These are virus infection, genetic effects, and hormonal status."

* * * * *

"Any animal that has a high incidence of 'spontaneous' tumours should be regarded as unsatisfactory. Not only is a positive result more difficult to establish in statistical terms unless large numbers of animals are used, but a positive result may fail to be elicited, thereby producing a false negative result. This is the most serious error of any system for detecting carcinogenic activity."

* * * * *

"The propensity of the mouse to produce tumours by the interaction of virus, genome, and exposure to chemicals, raises great difficulties of interpretation. Such interactions do not, as far as we know, play major roles in other species. These interactions may explain why the dose response to carcinogens usually observed in rats, is often absent or anomalous in the mouse, at least where the induction of lymphomata occurs (19,20). The ability to ascribe the relative importance in carcinogenesis of these various factors is often poor or non-existent, and in the case of bio-assays, as distinct from research investigations, usually impossible. Thus, extrapolation is not even feasible." (Crampton, S. 4–7)

Dr. James Jandl (Harvard Univ.) commented at length on the use of the mouse:

"In the proposed rules OSHA recommends the format of employing mice in numbers of approximately 50, including males and females; and rats, in similar numbers of males and females. Rats are not as susceptible, as a rule, to carcinogenesis as mice. However, a number of inbred strains of rats have been developed which possess similar spontaneous high rates of cancer of one or more organs. The characteristic of both inbred mice and rats is that they are mainly a very fragile, poorly breeding, congenitally defective group of animals, having a lifespan that is, on the average, approximately one-half to one-third of normal. The normal lifespan of a rat is between three and four years. The lifespan of a normal mouse is approximately the same. Mouse longevity among inbred strains is very difficult to obtain from the source laboratories. Rat longevity data are available and they range in inbred rats commonly used between eleven and fourteen months. The deaths in these animals are not necessarily due to neoplasm but through a variety of other defects that are clustered in their inheritance. These include nephritis, pneumonitis, pulmonary cysts, and central nervous system lesions, etc. Thus, these animals are susceptible to non-specific stimuli."

"An argument introduced early by OSHA in defense of the use of inbred animals, for which they have a particular liking, is that almost no carcinogenic agent known to affect man fails to affect inbred strains. One might add that it is possible to induce a cancer, many cancers, or to expedite the onset of spontaneous cancer in these inbred strains through very non-specific means. This is not very important proof, and involves very few chemicals, and does not apply to at least two carcinogens for man."

* * * * *

"Among the numerous overt biochemical and other differences between mouse and man which bear upon the issue of carcinogenesis, is a habit that is particularly prominent in rodents known as coprophagy. The significance of the coprophagy in the metabolism of ingested substances and specifically with regard to carcinogenesis has only been appreciated in recent years. It is generally accepted fact that a foreign chemical absorbed into the body of any mammal is subject to a host of detoxifying mechanisms, a typical one being conjugation to a glucoside, glucuronide or sulfate. This leads to excretion, harmlessly, of the compound through the bile into the intestine. At the lower end of the small intestine the conjugated material then is exposed to the vast population of anaerobic microorganisms which possess an enormous diversity of biochemical enzymic reactions, potentially."

* * * * *

"Consequently, the habit of coprophagy, which is an intense way of life for rodents, inevitably casts a shadow of doubt on much of the experimental carcinogenesis studies that have been performed in rats and mice. (Coprophagy cannot be prevented without

extraordinary physical technology; indeed, the restraints required to prevent it induce mental changes that totally alter the habits of the animal and make it useless as a test animal.)"

* * * * *

"It is highly unlikely that one can place credence upon the tests conducted in rodents, particularly inbred mice and inbred rats which are quite distant from man, which have different detoxifying and metabolizing properties, which have the unpleasant habit of coprophagy, and which have so short a life span that doses employed in testing them are hundreds or thousands or tens of thousands greater than those to which occupational personnel would be exposed. Indeed, it is almost certain that the high level of toxicity or the near-toxicity of each individual dose given on the unfirm and unsubstantiated ground that the lifespan of the animal must be compensated for by increased dosage in order to be interpretable for human beings, *contributes* to the carcinogenicity of any compound given. It is also true, in the opposite direction, that because large and toxic levels of compounds are tested, the multi-factorial dose-effect or dose-response nature of chemicals confuse the results and actually *conceal* a carcinogen because the chemical is given in an amount that in itself is anti-carcinogenic, as described previously."

"I think it would be reasonable to assume that a compound tested under these bizarre conditions in mice, should it be found to be carcinogenic, should be accepted only as a potential hazard for man until proved otherwise." (Jandl, S. 29–31, 33–34, 36–37 emphases added)

Dr. William Butler (NACA) also commented on this issue:

"It is true that the National Cancer Institute and Shell Research Company use mice extensively in their research. This is primarily for reasons of convenience, and because both mice and man are mammals. There is evidence that both mice and man are susceptible, for example, to the induction of hepatic carcinoma. But there is no good evidence that the responses of mice to carcinogens are similar to those of man. There are dissimilarities in the distribution and sites of neoplasms and there is no good evidence that the other pathological changes induced by carcinogens are the same in the two species. Such correlations have no foundation and should not be used to justify regulation.

"The use of mice has strongly been advocated as a test species for carcinogenesis bioassay. At the present time, this is beset with difficulties, as there is considerable disagreement over the pathological diagnosis of many lesions, not only those termed "hepatomas" but also on the significance to be placed on the increased incidence of such lesions in inbred strains." (Butler, S. 12)

As did Dr. Johannes Clemmesen (Danish Cancer Registry):

"OSHA proposes to accept as conclusive evidence of carcinogenicity positive results in one species if those results have been replicated. In doing so OSHA overlooks the fact that, in general, laboratory mice have been inbred more intensively than rats. Systematic brother-to-sister mating through many generations of mice has been encouraged to ensure a high degree of genetic uniformity. This, however, has resulted in a corresponding loss of general applicability of results. For instance, it has been possible to breed strains of mice with very high incidence of mammary cancer, while in the human species it is possible to demonstrate only a slight hereditary trend to this disease. In my view a strain of mice consisting of practically genetically uniform animals corresponds to the genetical makeup of only a single human and the data should be evaluated accordingly. Replication of results within the same strain of mice is not equivalent with replication within a non-inbred species, not to speak of different species. It therefore is not a sound criterion for classification." (Clemmesen, S. 12–13)

The above quotations mention a number of different objections to the use of specific strains of animals as the basis for inferences of carcinogenic risk. Although these objections were not always separated by the witnesses, the following distinct issues appear to be raised by this testimony:

(a) Can strains with a high spontaneous incidence of tumors be used in carcinogenicity testing?

(b) Does the presence of tumor viruses invalidate positive results in mouse test?

(c) Is the spontaneous incidence of tumors in certain mouse strains unstable, and if so does this invalidate positive results obtained in them?

(d) Can liver tumors in mice be diagnosed reliably and consistently?

(e) Is the induction of tumors in mice predictive of carcinogenicity in other species?

(f) Can reliable results be obtained in inbred strains of rodents?

(g) Are there other characteristics of rodents, such as a tendency to coprophagy, which would invalidate their use in carcinogenicity testing?

(a) *Can strains with a high spontaneous incidence of tumors be used in carcinogenicity testing?* This issue is discussed elsewhere in this Preamble (Section V.D. 7: *Spontaneous Tumors*). There OSHA concludes that the occurrence of spontaneous tumors in the strain of animals used for testing would not by itself invalidate a test, providing that the test is adequately controlled. Under such circumstances, the occurrence of a high incidence of tumors in controls is in general likely to give false negative rather than false positive results. OSHA agrees that in cases where the spontaneous incidence of tumors is extremely high (over 50 percent), the results of experiments may be difficult to interpret. However, although there was much discussion of *hypothetical* cases of this kind, no witness presented an example in which such a case was the primary evidence for carcinogenicity of a substance.

(b) *Does the presence of tumor viruses invalidate results obtained in mouse tests?* In addition to the general statements quoted above, three witnesses offered specific comments on viruses. Dr. Reginald Crampton (AIHC) presented the following comments:

"Cancer inducing viruses are widespread in mice, in particular those inducing tumours of the lymphoreticular system and the mammary gland (16). The genetic make-up of the mouse is also known to be a strong influence on the incidence of pulmonary, (17) mammary and lymphoreticular tumours. There is some evidence that in the case of lymphoreticular tumours it is the interaction between the genome and viruses which, in some ill-defined way, induces these tumours (18). Similarly, the susceptibility of the mouse to mammary tumours when its hormonal status is changed may also be related to the interaction of virus and hormonal activity and diet (16)." (Crampton, S. 6)

Dr. Robert Olson (St. Louis Univ.) also included a paragraph on viruses (Olson, S. 21–23). However, neither of these witnesses suggested that the effect of tumor viruses would be enhanced by noncarcinogens. The only such claim was made by Dr. Francis J. C. Roe (AIHC):

"The above concept of the origin of tumour viruses was advanced by ourselves ten years ago (Roe and Rowson, 1968) and is accepted as both plausible and likely by those who have considered it. It accounts for the fact that certain virus-induced neoplasms occur in far higher incidence in some strains of laboratory animal than any single kind of neoplasm of unknown cause occurs in any other species, including man. Thus there is no equivalent in the wild or in man of the 100% or close to 100% incidences of, say, mammary cancer, or malignant lymphoma in certain strains of mice, unless one encompasses outbreaks of leukaemia in fowls, epizootic myxomatosis (deliberately spread by man in the control of rabbit populations) and odd diseases, such as Aleutian disease of mink."

"It is clear from numerous published studies that the presence of tumour viruses may greatly enhance the risk of tumour development in response to exposure to other agents, including X-irradiation and chemical agents (see Roe and Rowson, 1968). Moreover, non-specific non-carcinogenic agents, such as turpentine (Friedewald, 1942) may greatly enhance the tumorigenic effects of tumour viruses." (Roe, S. 63)

As Dr. Roe pointed out, it is well-established that some *carcinogens* may interact with tumor viruses to enhance tumor incidence. The paper by Friedewald, cited by Dr. Roe for the proposition that non-carcinogens may do so also, was conducted under conditions (gross tissue damage followed by application of another carcinogen) which would be regarded by

OSHA as inappropriate for prediction of human risk. In any case, Roe's categorization of turpentine as "non-carcinogenic" is not justified by the results of any experiments available to OSHA (NIOSH, 1978c; USDHEW, 1969). This matter was put into perspective by Dr. Robert Squire (Johns Hopkins University):

"Since mice harbor so many oncogenic and other viruses, including a hepatitis virus, it has been claimed that hepatic neoplasms in this species are likely to be the result of cocarcinogenic viral effects that are not relevant to humans. Although it is true that mice are subject to numerous viral infections, so are humans. Furthermore, human hepatitis virus has been implicated in the etiology of human liver cancer (Ziegler et al. 1977). If, therefore, a murine virus is involved in mouse liver carcinogenesis (and there is no evidence to substantiate this), it may still be relevant to human cancer assessment." (Squire, S. 21)

Thus, OSHA concludes that the involvement of a virus in the etiology of a certain type of tumor would not necessarily invalidate the identification of a carcinogen based on observed induction of this type of tumor. However, to accommodate the scientific concerns expressed above, OSHA believes that if convincing evidence is presented showing the primary involvement of a virus in a particular experiment and that the substance is not likely to be carcinogenic in the absence of the virus, OSHA will consider the evidence on its merits if certain minimum criteria are met. Specifically, in other words, if the virus is clearly established to be the sole direct mechanism producing the carcinogenic effect in the test mammalian animals, the virus will not be regulated pursuant to this set of regulations, as the definition of "potential occupational carcinogen" found in 1990.103 includes only physical or chemical substances. If the substance is alleged to operate only by way of interaction with a virus, so that the substance has only an indirect link to the carcinogenic effect, the final set of regulations provide in § 1990.144(f) that:

"(f) *Indirect Mechanisms.*

The Secretary will consider evidence that positive results obtained in a carcinogenesis bioassay with experimental animals are not relevant to a determination of a carcinogenic risk to exposed workers, if the evidence demonstrates that the mechanism by which the observed tumor incidence is effected is indirect and would not occur if humans were exposed. As examples, evidence will be considered that a substance causes a carcinogenic effect by augmenting caloric intake or that the carcinogenic effect from exposure to a substance is demonstrated to be the result of the presence of a carcinogenic virus and it is demonstrated that, in either case, the effect would not take place in the absence of the particular carcinogenic virus or the augmented caloric intake.

(c) *Is the spontaneous incidence of tumors in certain mouse strains unstable, and if so does this invalidate positive results obtained in them?* Although a number of witnesses and participants referred to variability or "instability" in the spontaneous incidence of tumors in certain mouse strains, only a few such witnesses or participants provided detailed documentation of this variability and of factors influencing it. Dr. Francis J. C. Roe (AIHC) presented evidence that the "spontaneous" incidence of tumors may be influenced by genetic factors, viruses, hormones, microbiological status, immunological status, trauma, parasitic infections, radiation , caloric intake, and diet, in addition to carcinogens (S. 20–41). Dr. Roe placed particular emphasis on the roles of nutritional factors and caloric intake, and introduced some of his own experimental results in this area:

"Of all the factors known to influence the incidence of cancers, diet and caloric intake are, in my opinion, among the most important." (Roe, S. 31)

Dr. Robert Olson (St. Louis Univ.) also presented evidence for the influence of the same factors (S. 16–23), and in addition pointed out the dependence of tumor incidence on age (S. 21).

Drs. Paul Grasso and Reginald Crampton (AIHC) introduced their book "The Mouse and Carcinogenicity Testing" (Grasso *et al.*, 1977), which provided extensive tabulations of "spontaneous" tumor incidence in mice. The data were classified by strain, sex, site of tumor, laboratory and date of experiment. However, other factors stressed by other witnesses, such as age, duration of experiment, and diet, were not tabulated. The authors concluded:

"An important feature in the history of these tumours is the fluctuation in incidence in the same strain from generation to generation in the same laboratory, and from one laboratory to the next. This is particularly noticeable in both inbred and outbred strains with a high natural incidence of tumors. As far as one can tell, this fluctuation is unpredictable and quite unexplained." (Grasso et al., 1977, p. 6; Hearing Exhibit 138)

Some of the same data were cited by other witnesses, including Drs. Paul Newberne and Adrianne Rogers (MIT). A number of the same points were made in the book *Mouse Hepatic Neoplasia* (Butler and Newberne, 1975), especially in Chapter 6 by Grasso and Hardy:

"Thus there is some evidence that a number of factors may be involved in the induction of this type of tumour, and until more is known about their role it would be unsound to base conclusions on carcinogenic activity on the sole induction of mouse liver tumours, even assuming they are all cancers." (Grasso and Hardy, 1975, p. 129)

There was considerable confusion in this and other testimony on this subject. Most witnesses did not make clear whether they believed that the variations in "spontaneous" tumor incidence were in fact "unpredictable and quite unexplained" (as suggested by Drs. Grasso and Crampton) or whether they are in fact predictable and explainable on the basis of environmental and host factors (as suggested by the testimony of Drs. Olson and Roe). If the former, it would indeed be difficult to interpret the results of experiments which showed changes in tumor incidence at the sites in question; if the latter, the variability could be accommodated by the use of properly matched controls.

This issue was reviewed in detail by Dr. Walter Heston (NIH), an expert in the interaction of genetic and environmental factors in determining tumor incidence in mice, and the author of a number of papers cited by Drs. Olson, Roe, Grasso, and Crampton. Dr. Heston reviewed in detail the genetics of tumor incidence in mice, and the history of major strains and sub-strains, and he explained the phenomenon of "genetic drift". He then pointed out, with examples, the dependence of "spontaneous" tumor incidence on age, sex, hormonal status, diet, growth and well-being, and experimental factors such as postmortem conditions, degree of examination of animals, pathological definitions, and statistical fluctuations. He reviewed the data presented by Drs. Grasso and Crampton and pointed out numerous errors and over-simplifications. In particular, he pointed out that much of the "unpredictable and . . . unexplained" fluctuation in tumor incidence was attributable simply to variations in age of the animals in different experiments (Heston, Post-hearing Comment, Appendix 1). Much, if not all, of the remaining variation was attributable to genetic drift, inconsistencies in tumor classification, incomplete autopsy, and diet.

"Upon detailed examination of the background material contained in these publications it soon becomes apparent that the figures on tumor incidence are not easily comparable with one another and certainly do not demonstrate that there are wide and unpredictable fluctuations in tumor frequencies among animals likely to serve as experimentals and controls in a test for

chemical carcinogenesis." (Heston, Post-hearing Comments, p. 18)

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". . . do not find that this compilation establishes that tumors such as hepatomas vary in incidence in such a way as to lessen their value or the value of inbred mice in testing for carcinogenic effects of chemical substances." (*ibid.*, p. 17)

* * * * *

"The factors of age, substrain differences, diets, and procedures must all be controlled before any conclusions on variability of tumor rates can be drawn." (*ibid.*, p. 21)

Dr. Heston also pointed out similar errors and misinterpretations presented by Drs. Paul Newberne (MIT) and Robert Olson (St. Louis Univ.) (S. 21–23). Although the testimony of Dr. Heston (NIH) cited above was primarily addressed to the variability of liver tumors in mice, he also showed that the alleged variability in the incidence of mammary tumors was largely illusory (Heston, Post-hearing Comment, p. 21, Appendix 2).

As Dr. Heston pointed out, the effects of the environmental and host factors which affect tumor incidence in mice can readily be controlled by careful experimentation:

". . . there are many important genetic and environmental factors which are known to influence incidence of hepatomas and other tumors of the mouse. These influencing factors, both real and procedural, can make tumor frequency estimates of lessened or no value if they are not controlled by appropriate experimental designs. It is extremely important to recognize that these factors can be controlled and must be controlled in any adequate testing for a carcinogen. Control animals must always be run simultaneously with the experimental animals. The controls and experimentals must be genetically alike—preferably matched littermates within a well-characterized line of an inbred strains or F1 hybrid of two inbred strains. Controls and experimentals must be of the same age and sex distribution. They must be kept in the same environment to the extent that this is possible. This means that they should have the same temperature, humidity, lighting, and handling. Ideally cages should be distributed throughout the mouse room in a randomized way. The animals must be fed the same diet with the exception of the candidate carcinogen if a candidate compound is to be administered via the dietary route. Once the compound has been administered and the animals are sacrificed at the desired age or ages, controls and experimentals must be subjected to the same autopsy and diagnosis procedures. The only difference between the test group and the controls should be that the test group receive the candidate substance while the control animals are free of the candidate substance. In this way any difference between the two groups in incidence of hepatomas or other tumors can be attributed to the substance tested. While it is true that the incidence of induced or spontaneous tumors can be changed by environmental influences, induced changes in tumor incidence are not difficult to determine accurately if the environmental and genetic factors are properly controlled. *In other words, properly controlled carcinogenesis bioassays in mice give reliable and meaningful results."* (Heston, Post-hearing Comments, pp. 15–16, emphasis added)

Other witnesses (including Dr. I. Nathan Dubin (Medical College of Penn.), S. 19, and Dr. David Groth (NIOSH), Tr. 2999) concurred with Dr. Heston's conclusions. The National Agricultural Chemicals Association (NACA) also recommended that the same factors should be controlled (S. 33). Dr. Richard Griesemer (NCI) testified as follows:

"It is common knowledge that strains of rodents have differing incidences of spontaneous tumors. Also known, but not so commonly stated, is that the incidences of spontaneous tumors within a strain or substrain are remarkably constant. In a carcinogenesis bioassay, when matched control animals are used, genetic drift is not a factor. When matched control animals are housed under identical environmental and dietary conditions as well, comparisons of treated and untreated animals can be made with assurance." (Griesemer, S. 8–9)

Finally, as Dr. Heston (NIH) also emphasized, intra-specific variability in spontaneous tumor incidence, and influences of environmental and host factors on this incidence, are found not only in mice, but also in other animals, including humans:

"The assertion by Drs. Grasso and Crampton that chemically induced enhancement of the major tumors of the mouse (lung, liver, mammary and reticuloendothelial tumors) should not suffice to consider that chemical as posing a carcinogenic hazard to humans is a perplexing one. While it is true that such enhancement may come about by mechanisms which are not relevant to humans, it is also true that the same or related mechanisms may indeed operate in humans. Moreover, it is not known whether human tumors which do appear are "spontaneous", chemically-induced, or the result of chemical enhancement of a neospontaneous state in otherwise normal cells. Thus, I feel that a reproducible chemical enhancement of spontaneously occurring tumors can be considered as evidence that the chemical is hazardous to man—the chemical may indeed be carcinogenic in man.

"Studies of cancer incidence in human populations indicate that some cancers may be the result of chemical carcinogens acting on susceptible genotypes in people. Tokuhata (1963) and Tokuhata and Lilienfeld (1963) demonstrated this relationship between genetic susceptibility to lung cancer and clinical manifestation of lung cancer among smokers. A total of 270 lung cancer victims were matched with 270 controls who did not have lung cancer to the extent possible for age, smoking patterns, income, state of health, etc. A significant excess in lung cancer mortality was found in *relatives* of the lung cancer patients when compared with the relatives of the noncancerous control individuals. The question was raised about familial tendencies to smoke, which could be related to familial tendencies to develop lung cancer and thus give rise to a spurious association between smoking and lung cancer. It was found that lung cancer was aggregated in families independently of smoking habits and that smoking habits were also aggregated in families, but this aggregation was independent of the appearance of lung cancer. This is evidence that genetic predisposition to cancer, much like what we have observed in inbred strains of mice, may be critical in the chemical induction of cancer in humans." (Heston, Post-hearing Comments, pp. 23–25)

As many witnesses were at pains to point out, cancer incidence in humans is known to be influenced by genetic factors, viruses, hormones, microbiological status, immunological status, trauma, parasitic infections, radiation, caloric intake, and diet, in addition to carcinogens (see especially testimony of Drs. Roe, Squire, and the book edited by Fraumeni (1975)). These are exactly the factors listed by Roe (S. 20–41) as influencing tumors in mice and rats. Indeed, Dr. Crampton agreed that man is an "unsatisfactory" animal in the same sense as he had categorized the mouse as "unsatisfactory" (Crampton, Tr. 6590). "Satisfactory" or not, substantial evidence in the Record indicates that the mouse is a reasonable model for identifying substances that pose a potential carcinogenic hazard to humans. The critical precaution to be observed in experimental studies with mice—as in epidemiological studies with humans—is to match the exposed and unexposed (control) groups, so that rigorous comparisons can be made.

(d) *Can liver tumors in mice be diagnosed reliably and consistently?* Four witnesses presented evidence for the proposition that liver tumors in mice could not be diagnosed reliably and consistently, so that it is not possible to draw unambiguous inferences about carcinogenicity from changes in their frequency. This proposition has been presented in some detail in a book *Mouse Hepatic Neoplasia* (Butler and Newberne, 1975). This book was introduced into evidence by several parties, including its editors, Drs. William Butler (NACA) and Paul Newberne (MIT). In addition, Drs. Stan Vesselinovitch (NACA) and Adrianne Rogers (MIT) presented similar testimony.

The arguments of these witnesses and of contributors to *Mouse Hepatic Neoplasia* may be summarized briefly as follows: (i) Pathologists cannot agree

on the nomenclature to be assigned to tumors and other lesions of the mouse liver; (ii) most of the tumors are histologically benign, and the term "hepatocellular carcinoma" should be reserved for those that display unequivocal characteristics of malignancy; (iii) the progression of tumors through various stages is not yet understood, so that terminology implying a sequential development should not be used. In addition to these terminological questions, several witnesses claimed that the biological behavior of the tumors and their relationship to chemical carcinogens is not yet understood.

Examples of these statements include the following:

"It is evident from literature reports that there is a wide-spread divergence of opinion on the diagnosis of mouse liver lesions and of their significance (Butler and Newberne, 1975). At the I.A.R.C. Working Conference on Liver Cancer held at the Chester Beatty Research Institute in 1968 the problem of interpretation of focal proliferative lesions of mouse liver cells was discussed, and there was little agreement on the diagnosis of such lesions. The interpretation of individual lesions varied from hyperplasia to malignant neoplasia if invasion or metastases were not demonstrated. Without information on the biological behaviour of the lesions, pathologic opinions are based upon interpretation of histologic and cytologic detail and vary with the experience of individual pathologists."

"The divergence of pathologic diagnoses of mouse liver lesions has been demonstrated in two exercises. In an unpublished study, opinions were obtained from ten pathologists representing Canada, the United States, the United Kingdom, Germany and the Netherlands, on lesions induced in mouse liver by a pesticide. In no case was there unanimity of opinion of the ten pathologists consulted. In another study in Japan, a series of 43 cases was considered by 15 pathologists and again there was no unanimity of opinion. Moreover, there was a lack of consistency of individual opinions (Takayama, 1975). While in many cases there was a measure of agreement, in others wide variation was apparent."

"There are a number of explanations for these discrepancies including the inevitable disparity of training and experience of the pathologists. Whatever the cause of the disparity, it has far-reaching public health and economic significance. If the assessment of an experiment or test is based on the pathological interpretations of induced lesions, as it almost invariably is in safety testing, any disagreement in interpretation obviously limits the usefulness of the system." (Newberne and Rogers, S. 9–10)

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"As a result of my interest in the development and diagnosis of rodent hepatic neoplasia, and with the wide spread of disagreement as to the diagnostic features by which hepatic neoplasia is recognized in the rat and mouse, Dr. P. M. Newberne, Department of Nutrition and Food Science, Massachusetts Institute of Technology, and I decided that it would be useful to assemble a group of pathologists actively interested in the subject. As a result of our efforts, we organized a group of pathologists representing as diverse a range of opinion as possible to meet in a workshop and discuss the problem. This meeting was held in May, 1974, the report from which is published in a Monograph entitled 'Mouse Hepatic Neoplasia,' published by Elsevier (North Holland), Amsterdam, and edited by Dr. Newberne and myself. Within this workshop, many aspects of the problems of diagnosis and interpretation of mouse hepatic neoplasia were discussed. It will be apparent from reading the papers and from the discussion of this workshop that there are very wide levels of disagreement as to both the means by which hepatic neoplasia is diagnosed in the mouse and the relevance of this to carcinogenicity testing. It is also apparent that on the basis of the work which is in the scientific literature, the problems of diagnosis and interpretation cannot now be resolved." (Butler, S. 5–6)

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"Because of their frequent occurrence, the hepatic nodular lesions in rodents have been extensively studied and debated, yet these hepatic lesions in rodents persist as targets of controversy. Lesions whose natural history has been less well-studied cannot be characterized, and hence the significance of increased incidences of benign lesions in rodents is even more obscure." (NACA, S. 31)

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"We cannot conclude that each of various hepatic nodular populations, however temporally related to *bona fide* hepatocellular carcinoma, represent a development step committed ultimately to progress to hepatocellular carcinoma. In my judgment the carcinogenicity of a compound should be predicated upon the induction of malignant neoplasia (carcinoma) and not simply upon the induction of benign nodular lesions or even hyperplastic nodules in rodents. Provisions should be made by OSHA for consideration of evidence pertaining to the correctness of a diagnosis of malignant neoplasms, since this is directly relevant to the assessment of the potential carcinogenic risk to man." (Vesselinovitch, S. 13)

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"The study of neoplastic lesions in rodents is important for two reasons. Firstly to further the understanding of the pathogenesis of neoplasia and secondly as part of toxicological evaluation of new compounds. In both cases the extrapolation of the animal data to man must be based upon an evaluation of the information available. Therefore it is essential to attempt to get an accurate diagnosis of the proliferative lesions in the rat and mouse liver. The morphology and biological behaviour of these lesions in the rat has been described by many investigators. There is convincing evidence of a correlation between the structure of the primary lesions and its ability to invade and metastasize in the host. Also the incidence of metastases is high. In our experience with aflatoxin 75% of rats with such pleomorphic lesions have demonstrable invasion and metastases. Therefore a diagnosis of hepatocellular carcinoma on the morphology of the primary liver lesion is justified."

"In the mouse the situation is confused. There are only a few descriptions in the literature of the morphology of the lesions. There is even less published evidence of their biological behaviour in the host making any correlation between the morphology of the primary lesions and behaviour in the host unwise if not impossible. The presence of a 5% incidence of metastases from a defined lesion is insufficient evidence of the malignant nature of the remaining 95%. It can only arouse suspicion as to their nature." (Jones and Butler, 1975, p. 51)

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"The main problem that arises from the study of the nodular lesions in the mouse liver is making an assessment of their biological behaviour. It is obviously important to determine which of the lesions are carcinoma and to recognize the characteristics of the lesions which enables this diagnosis to be made. In the recommendations of the IARC Working Conference on Liver Cancer it was suggested that the assessment of the carcinogenicity of a lesion should be based upon its biological behaviour; that is the presence of invasion or metastases. However, in all published series and from our experience with phenobarbitone, the incidence of metastases is very low. Even in the reports (Walker et al., 1971) where the lungs were step serial sectioned metastases were only found in 2.1% of mice with nodules. In our own series we have so far failed to find any metastasis or evidence of local invasion. From literature surveys this would appear to be a common finding. Therefore, except in those cases where such biological behaviour can be demonstrated in a high incidence, the definitive diagnosis of carcinoma cannot be made."

"In the earlier part of this paper we have attempted to sub-divide the parenchymal cell lesions using the criteria of Walker et al. (1971). This classification was initially used as a convenient but arbitrary division. Walker et al. also found that the metastases occurred in those animals with the type B lesions. This classification was primarily based upon the structure of the nodules and its associated vascular bed and secondarily upon the cytology. At the extreme ends of the spectrum we find it reasonably easy to make the distinction between the types of lesions. However, there appears to be a continuous spectrum of change without a sharp separation of types. On our large area plastic embedded material the subdivision of types becomes even less certain."

"The cytological characteristics of the lesions have been used as diagnostic criteria of malignancy. In the large nodules arising in controls there is some variation in both cell size and staining characteristics of the cytoplasm, as well as increased variation in nuclear size. It is worth noting that in non-tumour bearing untreated mice, 18–24 months old, there is considerable variation in nuclear morphology. Multinucleate cells are also present and the nuclei contain cytoplasmic inclusions." (Jones and Butler, 1975, pp. 42–47)

It is apparent on reviewing this material that the issues raised were at least partly nomenclatural and semantic rather than biological. The classification of a continuous spectrum of lesions into discrete categories inevitably appears to be somewhat judgmental, and it is not surprising that pathologists should disagree as to the precise points at which to place the boundaries between categories. Much of the dispute is concerned with the distinction between benign and malignant tumors (see quotations above from Jones and Butler 1975, and a discussion of this paper in Butler and Newberne 1975, pp. 57–59). Most pathologists define a malignant neoplasm as one which has the *potential* to invade and/or metastasize, whereas others require that invasion or metastasis must have occurred before they consider a neoplasm to be malignant. The restrictive criteria demanded by Drs. Butler and Vesselinovitch for the diagnosis of hepatocellular carcinoma appear to represent extreme examples of the latter position. However, the nomenclatural distinctions between benign and malignant tumors are not important to the identification of potential carcinogenic risks, as discussed below in Section V.D. 6 of the Preamble. The important distinction for this purpose is not between benign and malignant tumors, but between neoplastic and non-neoplastic lesions. Although there are, of course some marginal cases on which pathologists will disagree, the consensus of the expert pathologists who testified at the hearing (with the possible exception of Dr. Butler) was that this distinction can be made reliably. For example, Dr. Robert Squire (Johns Hopkins University) testified as follows:

"Thus there is good evidence that the neoplastic process is sequential and therefore that the practice of differentiating early and late lesions and assigning them to different biological processes is arbitrary and without foundation. It is incumbent upon those who reject the presence of early lesions as evidence of carcinogenicity to provide evidence to the contrary."

"Pathologists have applied such names as hyperplastic nodules, adenomas, hepatomas, type A nodules, and hepatocellular carcinoma to the early proliferative nodules in mouse livers. NCI and NCTR pathologists involved in carcinogenesis bioassays and their collaborators currently agree that the early nodules should be termed hepatic adenomas, and the more diffuse, anaplastic lesions be termed hepatocellular carcinomas. The early nodules are considered benign neoplasms in the sense that they rarely invade normal tissues or metastasize at that stage, but they are recognized as the precursors of the malignant carcinomas. It is because of this potential for malignant behavior that several pathologists prefer the term carcinoma for the entire spectrum of lesions. There was, however, consensus among this group of experienced pathologists that all of the available evidence indicates that these proliferative hepatocytic lesions in mouse livers are neoplastic and represent a carcinogenic response in that species." (Squire, S. 20–21)

Dr. Melvin Reuber (NCI–FCRC) testified as follows:

"My own knowledge and experience of liver tumors in rats and mice are summarized in part in Appendix C, a review of carcinogenicity testing of chemicals with particular reference to organochlorine pesticides. This paper includes a description of the development of neoplastic lesions in the livers of rats and mice exposed to carcinogens, with a classification of successive stages in this development. For reasons stated in this and numerous other papers which I have written, it is my experience that neoplastic lesions in the livers of mice can be characterized and diagnosed as reliably in mice as in other animals. There is an excellent correlation between the histopathological characteristics of liver tumors in mice and their biological behavior as reflected by transplantation experiments or observations of invasion and metastasis. The development of liver tumors in mice closely parallels that observed in rats and humans. The induction of liver tumors in mice by chemicals is a reliable indication of carcinogenicity and provides a valid index of carcinogenic risk to exposed humans. This opinion is shared by specialists at the National Cancer Institute and the International Agency for Research on Cancer." (Reuber, S. 2, citing Reuber, 1977)

Dr. I. Nathan Dubin (Medical College of Penn.), after reviewing some of the data in *Mouse Hepatic Neoplasia* and pointing out the limited pathological experience of some of the authors, continued as follows:

"The argument has been made that we don't know enough about liver tumors in mice to correlate their morphologic structure with their behavior, and that the experience in mice has been limited to 25 years. Yet in 1908, Murray presented evidence attesting to the malignant neoplastic nature of the spontaneous hepatic tumor of the mouse, followed 7 years later by a report of its metastasis by Slye et al. in 1915 (cited by Stewart, 1975, p. 320). The duration of experience with mouse hepatic tumors is close to 70 years, and not 25 years." (Dubin, S. 17)

Dr. Harold Stewart (NCI), an eminent and experienced pathologist, discussed the issue at considerable length in one of his exhibits:

"Evidence attesting to the malignant neoplastic nature of the common spontaneous hepatic tumor of the mouse was first presented nearly 60 years ago (Murray, 1908); this was followed 7 years later by a report of its metastasis (Slye et al., 1915) and 20 years later by a report of its transplantability to other mice (Strong and Smith, 1936). Subsequent studies have continued to confirm these acceptable criteria of a malignant neoplasm in properly executed experiments. More than 30 years ago, Edwards et al. (1942) adduced additional evidence from elegant cytological studies that the spontaneous hepatic lesion of the mouse is a genuine neoplasm and advanced cogent arguments that contradicted those advanced by others who contended that the lesion is a hyperplastic nodule of regenerated tissue or a developmental anomaly. Among the arguments advanced then and now to imply the nonneoplastic nature of the hepatic growth is the high degree of differentiation of the cells, together with their definite tendency to form liverlike cords alternating with endothelial-lined sinuses and the capacity for storing fat and glycogen. That the lesion is regenerative in character is difficult to reconcile with the absence of any demonstrable damage in liver tissue away from the hepatoma. The fact that the lesion is seen in mice consistently after middle age contradicts the idea of a congenital anomaly. Moreover, the fact that the cells may be well-differentiated does not rule out neoplasm, since the metastasis of spontaneous hepatic cell carcinomas of man, the cow, and other species, and of certain of the induced liver carcinomas of the rat, may closely resemble normal hepatic cells."

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"It is evident from the foregoing that for years following Murray's 1908 report of the first observation of the common hepatic tumor of the mouse, this small neoplasm was the object of serious scientific study by those interested in the pursuit of knowledge for its own sake. Their studies resulted in the accumulation of a large body of facts dealing with the morphology of the spontaneous and induced tumors, the metastases and transplants, the characteristics of the subcellular constituents, the incidence in different inbred strains of mice, and the influence of genetics, age, diet, castration, and hormones. These scientific studies proved this lesion to be cancer. Then suddenly all this changed. This small tumor, often not as large as the tip of a man's finger, began to engage the attention of wealthy and powerful industrial concerns, the chemical and pharmaceutical companies in particular, whose products including drugs, chemicals, food additives, and pesticides when subjected to carcinogenicity testing in the mouse, might induce this tumor. Examples are aldrin, dieldrin, and DDT. Two questions were asked: Is the common liver tumor of the mouse a genuine malignant neoplasm? Should a chemical compound that induces the common liver tumor of the mouse but tumors at no other site in this species, and no tumors at any site in other species of laboratory animal, be banned from the human environment because the agent under test poses a carcinogenic hazard for man? There are those who have said yes and those who have said no to one or the other or both of these questions."

"Train (1974), in prohibiting the environmental use of aldrin and dieldrin (except for three minor uses), based his decision on the testimony of expert witnesses who are recognized authorities on

carcinogenesis and carcinogenicity testing. A crucial piece of testimony given by one of the experts, Dr. U. Saffiotti of the National Cancer Institute, was that the proposition is unacceptable, that the induction of liver tumors in mice is a tissue response that is not representative of carcinogenic effects such as are seen in the other organs and other species. Moreover, Train (1974) held that there is no distinction between the induction of so-called benign or malignant tumors in determining the carcinogenicity of a compound. Butler (1971) agreed that the ability of the hepatoma to transplant suggests that the lesion is neoplastic but not necessarily carcinomatous, since according to him transplantion per se cannot be considered an absolute indication of malignancy. Roe (1968) in a paper entitled "Carcinogenesis and Sanity" argued that evidence for carcinogenicity must be sought in more than one biological system since an increase of a type of tumor that arises commonly in a test species is suggestive of a cocarcinogenic rather than a carcinogenic effect. This opinion was later expressed by Roe and Grant (1970) and by Grasso and Crampton (1972). Fouts (1970) argued that the mouse is an unsatisfactory test animal because hepatic microsomal enzyme inducers, such as phenobarbitone and DDT, induce similar responses in man and the rat and a dissimilar response in the mouse. Some have dangerously proposed that a critical assessment of the carcinogenic potential to a man of a chemical compound, where variations in results between test species exist, can be obtained only from epidemiological studies in man exposed to high levels of the chemical for long periods. If this suggestion were to be taken seriously, then in view of the known lengths of the latent periods of different industrial cancers in man, such a wait-and-see attitude might well require a long period of many years before the onset of an epidemic of cancer due to the chemical in question manifested itself.

"Geliatly (1975) deplored the use of the term 'hepatoma' and instead advocated the use of the term 'hepatic parenchymal nodule' as though a change in name had the power to alter the nature of the lesion. He advanced the concept that the common liver tumor of the mouse represents a broad spectrum covering focal, nonneoplastic, cellular proliferation (nodular hyperplasia), benign parenchymal neoplasm (liver cell adenoma), and finally malignant parenchymal neoplasms (hepatocellular carcinoma). In analyzing the carcinogenic relevance of these different categories of hepatic lesions of the mouse to man, he classified 4-dimethlyaminoazobenzene as a powerful carcinogen for man because it induced hepatocellular carcinomas in the mouse according to his classification. By contrast, when he fed the food additives Flavour G and Flavour F he classified the increased hepatic lesions caused by these agents almost exclusively as small nodules of hyperplasia.

"The reasoning employed by some who classify the mouse hepatoma as a hyperplastic lesion is difficult to understand unless they mean to imply that such a lesion is a stage in the evolution of cancer. But not all authors imply this meaning. Geliatly (1975) is firm in his conviction that some hepatic lesions of the mouse are hyperplasias to begin with, and remain so and do not progress to cancer during the lifetime of the animal, but he adduced no convincing evidence to support this contention. As with many neoplasms of man and animals, the early stages of cancer may be innocuous-looking cellular proliferations. As the neoplastic condition progresses to its final stages, the lesion takes on patterns or appearances that pathologists commonly recognize as cancer. *What some do not appreciate is that the process is cancer from its earliest inception."* (Stewart, 1975, pp. 320, 328–328; Exhibit B to Stewart Statement; emphasis added)

Dr. Renate Kimbrough (CDC) similarly testified that so-called "hyperplastic nodules" in both mice and rats are neoplasms:

"Ms. Warren: Of what value in the determination of carcinogenicity do you think, for example, mouse hepatic neoplastic nodules would have?

"Dr. Kimbrough: To me they are part of the response that you get from an agent that is a carcinogen.

"Ms. Warren: What about hyperplastic nodules?

"Dr. Kimbrough: Of course, there is a lot of confusion still in the literature about that, and this same confusion exists for rat liver lesions. For the rat lesions the National Academy of Sciences is now trying to have a standardized nomenclature for these liver tumors to indicate what they represent. In other words, many people use hyperplastic and neoplastic nodules interchangeably. That is, one person will call something a hyperplastic nodule that another person will call a neoplastic nodule.

"To me, all of these nodules are neoplasms. There is no such thing as a hyperplastic nodule." (Kimbrough, Tr. 1792)

In confirmation of these expert opinions, it is interesting to note that a recently published study by Williams *et al.* (1979) has confirmed that both early and late stages in the development of mouse liver nodules are transplantable and thus conform to the criteria of neoplasms:

"In conclusion, the successful transplantation of the mouse liver nodules described in this study confirms that these nodules are neoplasms, and the finding of metastases from transplants of Type B tumors indicates that these are malignant neoplasms. These findings thus correspond with the biologic behavior of these neoplasms in situ recently described by Vesselinovitch et al. (Williams *et. al.*, 1979, p. 70)

OSHA concludes from analysis of these statements and exhibits that the alleged difficulty in identifying and interpreting neoplasms in the mouse liver is grossly exaggerated. The biological behavior of mouse liver neoplasms is well understood and can be identified objectively and reliably. Provided that scientific experience and judgment are used, the induction of mouse liver tumors can be used as an indicator of carcinogenicity as reliably as tumors arising at other sites or in other species. Indeed, one of the witnesses quoted above appears to have been essentially in agreement with this conclusion:

"For a number of years, I have advocated the usefulness of the mouse liver system for carcinogenicity bioassays when used with full consideration of the extensive knowledge acquired in the area of hepatocarcinogenesis and neoplastic liver morphology. This view is based on several, long-term, integrated studies aimed at identifying various factors and experimental conditions capable of modifying inception and/or promotion of liver carcinogenesis." (Vesselinovitch, S. 14)

(e) *Is the induction of tumors in mice predictive of carcinogenicity in other species?* As shown above, the objections to the use of the mouse liver tumor system on the grounds that it gives unreliable and non-reproducible results appear to have little or no substance. A separate objection made by some witnesses is that mouse liver tumors have unique characteristics which mean that enhancement of their incidence by a chemical is not predictive of carcinogenicity in other species, including humans. Although no witness made this claim explicitly, several made statements that at least implied such a position. Examples of such statements are those by Dr. Paul Grasso (AIHC), S. 5–10, Tr. 6560–6563; Dr. Reginald Crampton (AIHC), S. 7–8, Tr. 6559; Dr. William Butler (NACA), S. 12; and several statements by contributors to *Mouse Hepatic Neoplasia* (Butler and Newberne 1975). Although most of these comments were addressed to the mouse liver, Drs. Grasso and Crampton also objected to the use of other tumor sites in the mouse.

OSHA is aware that doubts about the validity of the mouse liver tumor system are fairly widely held, and that several reports of scientific committees issued in the past two years have reflected the controversy. For example, the Report of the NCAB Subcommittee made the following statement:

"Certain methods (listed below) are important pointers to potential carcinogenicity and cannot be ignored; however, they may require additional studies before extrapolation to particular conditions of human usage can be made. Examples of these methods are:

Bioassays employing inbred strains of animals which develop high incidences of particular tumors in the untreated state. In some of these studies the particular characteristics of the animals and the results obtained may require additional evaluation—in other instances, such well controlled test systems may be quite satisfactory for the

establishment of carcinogenicity of an agent." (NCAB Report, 1977, p. 462)

The International Agency for Research on Cancer (IARC) revised the wording of the preamble to its monograph series during 1978 to read as follows:

"Evidence for the carcinogenicity of some chemicals in experimental animals may be *limited* for two reasons. Firstly, experimental data may be restricted to such a point that it is not possible to determine a causal relationship between administration of a chemical and the development of a particular lesion in the animals. Secondly, there are certain neoplasms, including lung tumours and hepatomas in mice, which have been considered of lesser significance than neoplasms occurring at other sites for the purpose of evaluating the carcinogenic risk of chemicals to humans. Such tumours occur spontaneously in high incidence in these animals, and their malignancy is often difficult to establish. An evaluation of the significance of these tumours following administration of a chemical is the responsibility of the particular Working Group preparing the individual monograph, and it has not been possible to set down rigid guidelines; the relevance of these tumours must be determined by considerations which include experimental design and completeness of reporting."

"Some chemicals for which there is limited evidence of carcinogenicity in animals have also been studied in humans with, in general, inconclusive results. While such chemicals may indeed be carcinogenic to humans, more experimental and epidemiological investigation is required."

"Hence, 'sufficient evidence' of carcinogenicity and 'limited evidence' of carcinogenicity do not indicate categories of chemicals: the inherent definitions of those terms indicate varying degrees of experimental evidence, which may change if and when new data on the chemicals become available. The main drawback to any rigid classification of chemicals with regard to their carcinogenic capacity is the as yet incomplete knowledge of the mechanism(s) of carcinogenesis." (IARC, 1978, p. 21)*

The Food Safety Council made a similarly equivocal statement:

"There is controversy over the use of mice in toxicity testing, particularly with respect to the assessment of potential carcinogenic risk (Grasso, Crampton, and Hooson, 1977). The relevance of test results in mice is questioned primarily because of the high spontaneous rates of certain tumor types, and the effects of many modifying factors such as diet, viruses and hormones on the incidences. Particular concern is given to lymphomas, lung, liver and mammary tumors. It is true that certain strains of mice have high natural incidences of one or more of these tumors, and that their unusual genetic susceptibility may not be relevant to the human population. The use of such strains is appropriate for carcinogenesis research but not safety testing. However, several strains of mice have relatively low to moderate rates of spontaneous neoplasms and these are well suited to carcinogenicity testing. The fact that environmental factors may modify the tumor rates in test animals does not invalidate animal experiments unless species specific responses can be demonstrated, because similar factors undoubtedly also influence human response to carcinogens. The important point is that genetic and environmental influences be uniform among treated and control animals. It is also argued that mice are excessively sensitive to carcinogens, but one may equally argue that their sensitivity is an advantage in safety testing and in the extrapolation of animal data to the genetically diverse human population." (Food Safety Council, 1978, p. 98; Hearing Exhibit 227)

Finally, in the specific case of dieldrin, the WHO/FAO Working Group on the Evaluation of Pesticides in Food concluded that the induction of mouse liver tumors was not predictive of human risk:

"Results of various carcinogenicity tests in mice and other mammalian species indicate that there is a *species-specific effect of dieldrin and aldrin on the mouse liver,* resulting in an increased frequency of liver tumors only in this animal species. In all species examined (mouse, rat, rabbit, rhesus monkey, chimpanzee) 12-hydroxy-dieldrin and 4,5-aldrin-trans-dihydrodiol were the major metabolites. Regarding the ratios of these two metabolites the mouse seems to metabolize the test compound predominantly by the opening of the epoxide ring. This metabolic pathway on the one hand and a high rate of metabolism compared to other animal species examined on the other, could result in relatively high concentrations of 4,5-aldrin-transdihydrodiol in the mouse liver."

"Dieldrin, as well as other chlorinated pesticides, is a powerful inducer of microsomal enzymes. Owing to their high rate of metabolism, mice are especially susceptible to such effects. (See Section 3.1). Compared to other animal species, it reacts rather anomalously and the mouse, therefore, may not be an appropriate model for man in this case."

"The results of prolonged enzyme induction are proliferation of the endoplasmic reticulum in the cells, and hypertrophy and hyperplasia of the liver. These changes are fully reversible if treatment is ceased before tumours have developed on the chronically overloaded and damaged cells. Similar effects are produced by phenobarbital." (WHO/FAO 1978, exhibit 52).

The scientific documentation cited by these committees is much less extensive then that in the OSHA record. The NCAB and IARC did not cite any specific documentation on this issue, and the papers cited by the Food Safety Council and WHO/FAO have been discussed above and OSHA believes that other papers are more scientifically convincing.*

On reviewing the Record, OSHA finds that there is little scientific support for the position that tumorigenicity in the mouse is not predictive of effects in other species, including humans. In fact, there is extensive and substantial evidence in the Record to support the proposition that the induction of tumors in mice, and specifically tumors in the mouse liver, is highly correlated with carcinogenicity in other organs and other species. For example, Dr. Lorenzo Tomatis (IARC) (Tomatis, *et al.,* 1978; Appendix 5 to Tomatis Statement) reviewed data on chemicals or manufacturing processes associated with cancer induction in humans and reported that nineteen of these had been adequately tested in the mouse. Of these nineteen, eighteen were positive in the mouse, including five that were positive in the mouse liver and fifteen that were positive in other organs. The lone exception is hematite mining, for which the exact substance(s) responsible for inducing lung cancer are unknown. It is questionable whether exposure conditions similar to those found in the mining industry can be adequately recreated for laboratory tests to take into account possible synergistic effects.

An earlier review of the relationships between the induction of liver tumors in mice and effects in other species (Tomatis et al. 1973) was referred to by OSHA in the preamble to the proposed regulation. Dr. Umberto Saffiotti (NCI) described the results of this earlier survey:

"Tomatis *et al.* (1973) have reviewed this issue. They searched the literature and made a list of chemicals that were reported to have induced liver tumors in mice: 58 chemicals were included in this list. The literature was then examined for reports on tests of these chemicals in two other species, namely rats and hamsters. Of these 58 mouse liver carcinogens, 18 were reported to induce only liver tumors in mice, while the others produced tumors in other organs also. Of the 18 that were reported to produce only mouse liver tumors, *none* were reported to have been adequately tested in the other two species with negative results. Of the 58 chemicals which were reported to induce tumors of the liver, or of the liver plus other organs, in the mouse, only 16 were listed as having been tested and found negative in one of the other species (rats or hamsters)#of these 16, however, 9 were reported as negative in rats but were not tested in

* Some confusion was caused in the Record by the introduction of an earlier draft of this section of the preamble. Such confusion was evident, for example, in the testimony of the American Textile Manufacturers Institute (S. 15). OSHA notes that the revised and final version quoted above does not draw any general conclusion about the applicability of results obtained in the mouse liver, but merely states that these neoplasms "have been considered of lesser significance" and states that such cases should be examined on their own merits.

*See also NIOSH (1978b) for a much more comprehensive and critical review of the data on aldrin/dieldrin cited by the WHO/FAO committee.

hamsters, 1 was reported as negative in rats but was positive in hamsters, 5 were reported as negative in hamsters but were positive in rats. Thus only one compound, positive in mice, was reported as having been tested in both rats and hamsters with negative results: This compound is benz(a)anthracene which was reported to cause not only hepatomas but also lung tumors by feeding in mice, and was found to be carcinogenic also by other routes of administration in mice, causing tumors of the lung, skin, and bladder. Although this compound was reported as negative in rats and hamsters, it is important to state that it was *not adequately tested* in rats and hamsters. There are no reports of such tests by chronic feeding in rats or hamsters, nor of any long-term tests with continuous administration in large numbers of animals, with adequate pathology. The only feeding study in rats on this compound was published in 1945 (White and Eschenbrenner, 1945); it stated that 2 out of 3 male rats were found to have 3 hepatomas each. No hepatomas were found in 3 females, nor in different groups of controls. Although obviously totally inadequate, this report suggests the possibility of liver carcinogenicity in rats. So the conclusion of this literature survey is that no chemical was found to have been adequately tested and shown to produce liver tumors in mice but no tumors in the other two most common species of test animals. As a matter of interest, Tomatis et al. have limited their discussion to the correlation of test results as presented in the literature, without undertaking a critical evaluation of the adequacy of the test used to enter a classification of positive or negative into their tables. Such an analysis would show that many tests in rats or hamsters, reported as negative, are really quite inadequate and should not be accepted as (negative evidence)." (Saffiotti, S. 32–33)

Dr. Saffiotti concluded:

"The survey by Tomatis *et al.* is however, sufficient to disprove the proposition that the induction of liver tumors in mice is a tissue response that is not representative of carcinogenic effects such as are seen in other organs or other species. No scientific basis could be found to support the suggestion that the carcinogenicity of a chemical in mice is not representative of its activity in other species including man." (Saffiotti, S. 33)

The review by Tomatis *et al.* (1973) has not been updated to incorporate the results of more recent experimentation. However, the data introduced into the record do not justify any change in the general conclusion drawn by Tomatis *et al.* and by Dr. Saffiotti. In the NCI bioassay report series, several new chemicals have been reported to induce tumors in the mouse liver but not in other organs of the mouse or in rats. Examples are DDE, trichloroethylene, chlordane, and heptachlor (NCI Carcinogenesis Technical Reports, Nos. 2, 8, 9, 131). On the other hand, several chemicals which have been reported in the past to be carcinogenic only in the mouse liver are now known to induce tumors also at other organs in the mouse and/or in other species. Examples are DDT (NIOSH 1978a), aldrin/dieldrin (NIOSH 1978b), phenobarbital (Rossi et al. 1977), and chloroform (NCI Carcinogenesis Technical Report, 1976). Thus, as experimentation continues, the general concordance between the mouse liver and other bioassay systems remains good.

The validity of results obtained in the mouse for assessing carcinogenic potential in humans was also supported by a number of other eminent scientists. These included: Dr. Harold Stewart (NCI), S. 5; Dr. Samuel Epstein (Univ. of Ill.), Exhibit 10c, p. 2429–2431; Dr. Arthur Upton (Director, NCI), S. 18; Dr. Curtis Harris (NCI), Tr. 2003; Dr. Benjamin Trump (Univ. of Md.), Tr. 2002–2003; Dr. Lawrence Fishbein (NCTR), Tr. 1857; Dr. Melvin Reuber (NCI-FCRC), S. 2; Dr. I. Nathan Dubin (Medical College of Penn), S. 17–21; Dr. Robert Squire (Johns Hopkins University), S. 22; and Dr. Renate Kimbrough (CDC), Tr. 1797–1798. And, based on similar scientific evidence, the Administrator of EPA, on at least two occasions, has come to the same conclusion. In *In Re Shell,* the EPA Administrator stated:

"Most of what we know about cancer is derived from tests with experimental animals, usually mice. The response of mice to carcinogens is similar pathologically to that of man; and research laboratories, such as those of the National Cancer Institute and Shell Chemical Company, use mice extensively in their research." (Footnotes omitted)

And in *In Re Velsicol,* the EPA Administrator reiterated:

"For these reasons, pesticides and other chemicals are tested for carcinogenicity in laboratory animals, particularly mice (the first choice) and rats, which are broadly accepted by the scientific community as appropriate test animals for these purposes."

"The mouse develops almost every kind of cancer that occurs in man and, with few, if any, exceptions, is subject to cancer from any source which is known to be a carcinogen in man. In both mouse and man, genes are involved in the control of processes through which cancer is induced. They control reactions to physical and chemical carcinogens. The genetic characteristics of mouse and man are sufficiently similar to permit the assumption that if a chemical or other agent such as radiation causes cancer in a particular organ of mice, then it will also cause cancer in the same organ, or possibly some other organ, of man.

"In fact, the difficulty with using laboratory animals to test for carcinogenicity lies in the other direction. The failure of a chemical to induce cancers in a particular strain (or even several strains) of laboratory animals is not an assurance that the chemical is not a carcinogen in man, since that particular strain may be genetically resistant to cancer from that source, where, by contrast, the genetic susceptibility of people to cancer varies a great deal from person to person." (42 FR 54160)

(f) *Can reliable results be obtained in inbred strains of rodents?* Several witnesses objected to the use of inbred strains of rodents, specifically mice, on the grounds that such strains were excessively sensitive, unstable, or otherwise unsuitable for carcinogenicity testing. The most explicit set of objections of this kind was by Dr. James Jandl (Harvard Univ.):

"The arguments presented by OSHA in defense of their reliance upon testing substances for carcinogenesis in inbred strains of mice are specious and often contradictory. For example, it is stated that almost all substances accepted as being carcinogenic for human beings are carcinogens for 'rodents'; the fact is that the strains of mice most commonly selected for such tests have a spontaneous development of one or more cancers as a natural consequence of the particular genetic defect in cancer resistance mechanisms for which they were originally inbred."

* * * * *

"In the proposed rules OSHA recommends the format of employing mice in numbers of approximately 50, including males and females; and rats, in similar numbers of males and females. Rats are not as susceptible, as a rule, to carcinogenesis as mice. However, a number of inbred strains of rats have been developed which possess similar spontaneous high rates of cancer of one or more organs. The characteristic of both inbred mice and rats is that they are mainly a very fragile, poorly breeding, congenitally defective group of animals, having a lifespan that is, on the average, approximately one-half to one-third of normal. The normal lifespan of a rat is between three and four years. The lifespan of a normal mouse is approximately the same. Mouse longevity among inbred strains is very difficult to obtain from the source laboratories. Rat longevity data are available and they range in inbred rats commonly used between eleven and fourteen months. The deaths in these animals are not necessarily due to neoplasm but through a variety of other defects that are clustered in their inheritance. These include nephritis, pneumonitis, pulmonary cysts, and central nervous system lesions, etc. Thus, these animals are susceptible to non-specific stimuli.

"An argument introduced early by OSHA in defense of the use of inbred animals, for which they have a particular liking, is that almost no carcinogenic agent known to affect man fails to affect inbred strains. One might add that it is possible to induce a cancer, many cancers, or to expedite the onset of spontaneous cancers in these inbred strains through very non-specific means. This is not very important proof, and involves very few chemicals, and does not apply to at least two carcinogens for man." (Jandl, S. 24, 29–31)

Dr. Robert Olson (St. Louis Univ.) citing Roe and Tucker (1973), likened the

use of "pure bred strains of mice with high tumor incidence as tantamount to using a dirty biological 'test tube', in which case the carcinogen may in fact be functioning as a co-carcinogen." (S. 15). Dr. Benjamin Van Duuren (NYU) expressed a preference for using random-bred animals which have a low incidence of spontaneous tumors, and commented on supposed difficulties raised by the use of inbred strains in the NCI bioassay program (Van Duuren, Tr. 1814–15).

These comments reflect considerable confusion about a number of points. For example, OSHA did not have a "particular liking" for inbred strains, nor recommend their use: OSHA merely proposed to use results obtained in either inbred or outbred strains if such were the only results available. Inbred strains do not constitute a "dirty" experimental tool, but a "clean", precise tool for a limited purpose. The point is that some witnesses in the hearing confused the interpretation of tests which demonstrate hazard with the design of tests to demonstrate safety.

This issue was reviewed by Dr. Walter Heston (NIH), a pioneer in the development and use of inbred strains of mice for studying factors affecting tumor incidence. Dr. Heston described characteristics of inbred strains of mice which were misunderstood by the witnesses quoted above:

"An inbred strain is a line or breed of mice which has been propagated by matings of littermate brother sister pairs for 20 or more generations."

* * * * *

"After 20 generations, the percentage of homozygosity increases very slowly until it is balanced by the reverse tendency toward heterozygosity because of spontaneous mutations. This reversion to heterozygosity is the basis for the process known as genetic drift which is discussed below.

"In starting an inbred strain, problems in maintaining the strain soon arise because of the appearance of deleterious traits. Most individuals of all diploid species contain genes for recessive deleterious traits. These traits are not expressed because they are masked by the dominant nondeleterious alleles. During inbreeding, recessive genes become expressed because of homozygosity. Frequently these deleterious traits cause loss of viability, reproductive success, or both. These problems in viability are overcome, however, by maintaining large numbers of animals. This permits selection for vigorous animals. The critical period is around generation eight. Once the strain gets beyond this point it usually can be maintained with no difficulty.

"With homozygosis at practically all loci the strain continues to breed true generation after generation. All offspring are then genetically similar to one another and to their parents. The degree of genetic similarity is almost as great as that between identical twins.

* * * * *

"Today we have inbred strains of all laboratory animals that supply the genetically controlled material with which the most modern medical research on mammals is carried out. Without the use of inbred strains, biological results would be much more difficult to reproduce, which would lessen their value.

"1.2 Tumor frequencies in mouse strains and substrains

"In selecting the brother and sister pairs which are the basis for developing an inbred strain, certain traits, such as viability, are selected intentionally. The majority of traits, however, are fixed unintentionally in the inbreeding process. Such traits include those which are responsible for fixing the incidence of various tumors that can be expected when nongenetic factors are controlled. Thus certain combinations of genes give, in some strains, over 99% of certain tumors within the normal lifespan of the animals. Other gene combinations, seen in other inbred strains, give incidences approaching 0% and still other strains have tumor incidences in between these extremes. These incidences are characteristic of the particular strain and are relatively stable generation after generation, provided the nongenetic factors are kept constant." (Heston, Post-hearing Comments, p. 1–4)

After reviewing data on factors which affect tumor incidence in inbred and outbred strains, Dr. Heston concluded:

"The human population is a genetically heterogeneous one in which some individuals may be expected to be resistant to induction of particular tumors and some may be genetically susceptible. We might not have to be concerned about the resistant individuals, and they might constitute a large part of the population. Unfortunately we do not know who is susceptible, who is resistant, and what proportion of the population falls into these groups. If a compound induces tumors in a susceptible strain such as C3H, then it probably can induce tumors in susceptible humans as well, and exposure to such a chemical should be avoided." (*ibid.*, p. 27)

Similar views were expressed by other witnesses, such as Dr. Arthur Upton (Director, NCI), S. 14; Dr. Richard Bates (NIEHS; FDA), S. 15; and Dr. Richard Griesemer (NCI), S. 8–9.

OSHA concurs with these witnesses' assessment of the scientific data presented on this issue. The evidence indicates that both inbred and outbred strains of mice have advantages and disadvantages. The use of inbred strains permits the precise experimental analysis of carcinogenic phenomena, at the expense of loss of generality. The use of outbred strains has the advantage of being more easily extrapolated to a genetically heterogeneous population, at the expense of loss of statistical sensitivity. OSHA therefore intends to use results obtained from both types of systems, while recognizing and taking into account the limitations of each.

(g) *Are there other characteristics of rodents which would invalidate their use in carcinogenicity testing?* The only other specific characteristic of rodents which was explicitly proposed as a factor which might invalidate positive results for carcinogenicity obtained in them was their tendency to coprophagy. Dr. James Jandl (Harvard Univ.) presented the hypothesis that microbial action on chemicals in rodent feces might transform chemicals into active metabolites that would not be formed *in vivo* (S. 33–36).

On reviewing this argument OSHA does not find it convincing. The chemicals cited as examples by Dr. Jandl are well-established as carcinogens in more than one species (IARC Monographs). It is highly improbable that they would not be metabolized to carcinogenic derivatives *in vivo*, either by the gut flora or enzymatically, (see comments by Dr. Roe, S. 27, and Dr. Goldberg, Tr. 6512). To establish this fact would be extremely difficult (see discussion of Metabolism below).

c. OSHA's Conclusions

After reviewing all the material and evidence submitted into the Record on this issue, OSHA concludes that there is no substantial scientific evidence to support the proposition that tumors induced by substances in properly controlled experiments in mice should be given less weight than tumors induced in rats or other mammalian species. In any event, prudence would appear to prohibit a regulatory agency from ignoring experiments in mice, pending the development of much greater scientific knowledge on this issue than presently exists. Most of the discussion above has been specifically concerned with liver tumors in mice, because the liver is the site on which most of the objections to the use of mice have been focused. However, most of the arguments summarized above are equally applicable to other tumor sites whose predictive value has been questioned, such as the lung, mammary gland, and lymphoreticular system of mice. This is equally true for certain types of tumors in other species, such as mammary tumors in rats. OSHA concludes that in all these cases, the arguments for the hypothesis that mice have unique characteristics that would make the results inapplicable to other species are scientifically unconvincing. With reference to the disputes over pathological nomenclature, Dr. Harold

Stewart (NCI) placed these arguments in perspective:

"Decisions about the pathologic classification of lesions that arise in animals subjected to tests for carcinogenesis may therefore have far-reaching legal and social implications. A critical factor is the skill and dependability of the pathologist who evaluates the end results. If, for example, he diagnoses the induced lesions as cancer, the agent is banned. If, on the contrary, he categorizes them as a hyperplastic process or a benign tumor, there is the possibility that the agent may not be banned from the environment. Despite the fact that no immutable histologic criteria exist for the certain determination of the early cellular prolifefations of cancers as purely hyperplastic changes, there are those who have advanced specious arguments in favor of this contention. Another ploy is to lower the value of the diagnosis of cancer to benign tumor, to classify for example, the murine alveologenic carcinoma of the lung as adenoma and hepatocellular carcinoma as hepatoma or a space-occupying nodule—this even though the neoplasms may metastasize in from 1 to 20% of tumor-bearing animals. There is, moreover, no basis for classifying the so-called mammary fibroadenoma of the rat as a benign tumor, because, in reality, it is a neoplasm in a stage of transition: it readily transplants to syngeneic animals in which it may grow as a sarcoma or carcinoma or a mixture thereof.[13] Further, some who apply the terms "adenoma", "hepatoma," and "fibroadenoma" to these respective neoplasms downgrade the classification of the chemicals that induced them to tumorigens and contend that tumorigens are less harmful to man than are carcinogens. In my opinion, *those who express these views fit the definition of a dialectician: they are practiced in the art of using forms of reasoning so as to make fallacies pass for the truth."* (Stewart 1977, pp. 310–311, Exhibit C to Stewart Statement, emphasis added)

Based on the detailed scientific evidence in the Record, OSHA reaffirms its proposed position, namely that data from all mammalian species, including the mouse, will be relied upon in the qualitative identification of potential carcinogens.

2. Positive Versus "Non-positive" Results

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA proposed that, in general, positive results should supersede non-positive or negative results:

"Likewise, positive results in tests with experimental animals, if obtained under sound experimental conditions and with proper statistical confirmation, should generally supersede negative results, both because of the aforementioned insensitivity of laboratory bioassays conducted with limited numbers of animals, which may frequently lead to false negative results, and also because of interspecies differences in susceptibility. (42 FR 54161)

In support of this proposal, OSHA relied upon two sets of recommendations. First, several expert committees had specifically recommended this approach:

"Evidence of negative results, under the conditions of the test used, should be considered superseded by positive findings in other tests. Evidence of positive results should remain definitive, unless and until new evidence conclusively proves that the prior results were not causally related to the exposure. (NCI Ad Hoc Committee, 1970, p. 1; Exhibit 10b to Epstein Statement)

Similar recommendations were made by other committees (UICC 1969, p. 18; NCAB 1977, p. 463). Second, expert committees which had specified minimum requirements for safety testing had recommended testing in at least two species because of the likelihood of obtaining false negative results in single tests (WHO Tech. Report 220, p. 8; Mrak Commission, pp. 486–487; the Surgeon General's Ad Hoc Committee, 1970, p. 1).

b. The Public's Response and OSHA's Evaluation

At the outset, it should be noted that the issue of positive and "non-positive" data, presumably conflicting with one another, arises in three basic contexts, namely: (a) positive animal evidence and "non-positive" human evidence; (b) positive and "non-positive" animal evidence in the same animal species; and (c) positive evidence in one animal species and "non-positive" evidence in another animal species.

(1) *General Support for the Proposed Position.*

Dr. Arthur Upton (Director, NCI) made the following statement:

"Given this lack of knowledge concerning mechanisms, I believe that a reproducible carcinogenic response in *any* species of test animal must be considered sufficient to describe the test compound as a carcinogen and so a potential threat to human health. I consider that a similar reaction in a second mammalian species is a confirmation of the carcinogenicity of the test agent, but it is not necessary before a finding of carcinogenicity and potential threat to human health can be made: negative results in a second or even third species of test animal do not in my mind establish that the test agent is not a potential threat for human beings. Given the variation in human susceptibility to carcinogens, I believe it unreasonable to ignore a finding of carcinogenicity in any mammalian test species when considering possible effects on human health." (Upton, S. 17)

Dr. Umberto Saffiotti (NCI) quoted the "expert" 1970 Ad Hoc Committee on Evaluation of Low Levels of Environmental Chemical Carcinogens:

"Conclusive evidence of carcinogenicity in one species supersedes negative findings in other species in the extrapolation of risk to man, since no basis presently exists to rule out the likelihood that human beings respond in the same manner as the positive test species." (Saffiotti, S. 34)

Dr. Roy Albert (EPA) made the following statement:

"Well, I think it is very difficult to define this in an explicit way, because the large number of combinations and permutations of the number of studies that one can have, the kinds of responses that one sees in the positive, and also in the negative as to whether they are really negative or marginally so, how well the studies are done. I suppose one could come up with some sort of scheme for doing this, but it seemed to me that when one has a clearcut study that is positive it is difficult to see how negative studies are going to eliminate that positive result." (Albert, Tr. 2379)

Dr. Robert Squire (Johns Hopkins Univ.) cited the NCI Temporary Committee for the Review of Data on Carcinogenicity of Cyclamate in discussing the scientific judgment which must be exercised in each individual case and concluded:

"Our current test methods are relatively insensitive and imprecise for detecting carcinogenic potential. However, any clearly positive animal study must be considered as the best qualitative experimental evidence available for human carcinogenic risk." (Squire, S. 13)

Dr. Adrian Gross (FDA) commented:

"I would also endorse the concept stressed several times in the document that, if the principle of statistical significance is retained, in cases of repeated investigations with apparently conflicting results, unequivocal findings of carcinogenesis should not be "averaged" with the more questionable ones without giving the former a great deal more "weight" than the latter." (Gross, S. 2)

Dr. Robert Hoover (NCI) in discussing human studies, laboratory animal assays, and *in vitro* assays commented:

"Because of the severe limitations of each of these methods of investigation, a good study showing positive evidence of carcinogenicity should take precedence over negative studies. For example, animal studies are hindered by the inability to routinely evaluate the effect of low-level exposures, and the potential problems of species specificity. On the other hand, human studies are hindered by the inability to identify low-level, but substantial, increases in risk, the long latent period between exposure and disease, and the influences of multiple exposures and differing host susceptibilities." (Hoover, S. 20)

General support for the proposition that positive animal data should, in general, supersede non-positive animal data was also presented by the

Scientific Apparatus Makers Association (S. 4) and by other parties.

(2) *Issues Raised in the Rulemaking.*

(a) *In General.* Despite the general support for OSHA's proposed position, a number of witnesses objected in principle to the discarding of non-positive evidence. For example, the American Iron and Steel Institute argued as follows:

> While it may very well be that, in most instances, positive animal data should outweigh negative animal data, in the view of Drs. Snyder and Triolo, it is bad science and bad regulatory policy to establish a rule that positive animal results must be preferred over negative animal results in *all* cases, without evaluating each experiment to determine its scientific merit. This is particularly true since positive animal results are not invariably indicative of human carcinogenicity. (AISI, S. 26–27)

Dr. Gerald Chase (Johns-Manville) voiced a similar view during his oral testimony:

> Positive results should not generally supersede negative results. Such an approach represents analysis of available information at an elementary level. As with risk assessment, OSHA should use the most advanced scientific input in assessing negative and positive studies. While on the one hand positive studies certainly cannot be blindly counterbalanced by negative studies, neither, on the other hand, can negative studies be ignored when a positive study is available.
>
> Both approaches are scientifically, statistically naive . . . OSHA must allow for sophisticated, not naive, analyses of data. Positive results should not generally supersede negative results, from a statistical point in view. (Chase, Tr. 4855–4856)

AIHC asserted that OSHA was forming its policy merely for administrative ease:

> "While as an administrative matter it may be convenient to reject negative results in the face of a positive test, the record demonstrates that any such conclusion is inconsistent with the scientific evaluation process." (AIHC, Post-hearing Brief, p. 159; Hearing Exhibit 251)

Other comments presented by different industry representatives were typified by the comment of PPG Industries:

> "The basic philosophy that studies revealing positive findings are either more reliable or properly conducted fails all scientific principles. A positive finding in an animal toxicity study must be equally critiqued according to the same guidelines as would be a negative animal study." (PPG Industries, S. 3).

Similar comments were presented by: National Paint and Coating Assoc., S. 14; FMC, S. 9; Ciba Geigy, S. 7; Pennzoil Co., S. 6; Chemical Industry Institute of Toxicology, S. 2; Eli Lilly and Co., S. 4; Texaco, Attachment 1; NACA, S. 17; Standard Oil, S. 11; Council for Agricultural Science and Technology, S. 17–19.

The specific issues raised by the testimony of these witnesses and other participants were the following:

1. Should "non-positive" results in human studies outweigh positive results in animal experiments, and if so, in what circumstances?
2. Should "non-positive" results in animal experiments outweigh positive results in other animal experiments, and if so, in what circumstances?
3. What precautions should be taken to avoid placing weight on "false positive" results?
4. How should OSHA deal with data of varying quality?

In this section, we review and analyze the scientific evidence presented on these issues.

(b) *Should "non-positive" results in human studies outweigh positive results in animal experiments?* Many witnesses argued that, in principle, results from human epidemiological studies should be given primary weight, and that non-positive human data should generally or always outweigh positive animal data. However, very few actual examples of such situations were presented, and none of these were borne out when scrutinized, as pointed out above. The question of "non-positive" human epidemiological studies has been discussed above (See Chapter IV. *Evidence Derived from the Human Experience*).

The remaining discussion in this section refers only to the situation in which positive and non-positive results in animal experiments exist and must be evaluated together.

(c) *Should "non-positive" results in animal experiments outweigh positive results in other animal experiments?* The general principle underlying OSHA's proposed position is that animal experiments are insensitive, so that "false negative" results are likely to be frequent. This principle was supported by many witnesses, a sample of whose testimony follows. Dr. Joyce McCann (Univ. of Calif.) testified as follows:

> "The confidence with which one accepts a negative is less than the confidence that one accepts a positive. I mean, I think that is clear in any scientific experiment.
>
> "With respect to, for example, comparing animal cancer test data and short-term test data, a negative in an animal cancer test means more to me than a negative in a short-term test. But it is very difficult to prove a negative. I do not think we can get away from that fact. It is very difficult.
>
> "A negative animal cancer test can only tell us that a chemicial is less potent than a certain lower limit of detectability value, depending on the particular design of that test. Now, that less potent includes zero, so that includes all the non-carcinogens, but it also includes the mistakes. But that is something we cannot get around.
>
> "The National Cancer Institute has tried to define what seems to constitute a reasonable cancer test that is economically feasible and has a chance of detecting a fairly weak carcinogen, but such tests can make mistakes. They can still miss things, especially the very weak carcinogens.
>
> "That is not to say that everything that is negative in a cancer test is likely to be positive. It is just the opposite." (McCann, Tr. 1590)

Dr. Donald Kennedy (Commissioner, FDA) pointed out that any errors in experimentation are likely to result in a non-positive outcome:

> "As to negative results in animal tests, you said "better conducted." I would have to know how better conducted. The general experience is that when you mess up a study it is easier to make it come out negative than positive. There are all sorts of places in science where we employ that principle. Indeed, when you design an experiment, one of the features of the design that you try to build into it is that the kinds of mistakes you are likely to make are going to be mistakes that will conduce to the results you are not getting. In other words, you try to design the experiment so that experimental error will not tend to prove the hypothesis.
>
> "It just turns out that with most animal studies the results of error are more likely to make a substance come clean than to show that it is carcinogenic. At least, I think that is the view of most people who have been involved in such experiments. I mean, if you mess up on feeding the animals, if you put them in the wrong cages, if you screw up their diets, you are going to make the experimentals and the controls more alike, because you are going to reduce separation. So there is a real rationale for taking positive results more seriously than negative results." (Kennedy, Tr. 571–572)

Drs. Curtis Harris (NCI) and Benjamin Trump (Univ. of Md.) commented on the insensitivity of test systems:

> "Dr. Harris: The test systems, including epidemiological data, are extremely insensitive; therefore, one cannot necessarily trust negative data, which is unfortunate.
>
> "Dr. Trump: And that is especially true with epidemiologic data because of the difficulties and complexities." (Tr. 2028)

They expanded upon these points upon further questioning:

> "Dr. Harris: If they are positive (results of test), you have indication under the conditions of test that the result that you have, whether it is toxicity, mutagenicity, carcinogenicity, is positive. If it is negative, you do not know. The test may be inappropriate; you may be choosing the wrong animal; you may be choosing a whole variety of different things.

"Dr. Trump: The important point of the testing is to identify hazards, and then to regulate. It is true there may be some additional hazards in the so-called negative group." (Tr. 2034)

An experiment's sensitivity is a trade-off between how small an increase in carcinogenicity the researcher wishes to be able to detect and how large an experiment he or she can practically manage to run. Dr. David Rall (Director, NIEHS) addressed this compromise in his oral testimony:

"If you look at the broad spectrum of animal experiments for carcinogenesis, what you really want to do is detect positives. You cannot design a large enough experiment to exclude beyond all sorts of probability a negative. What you really want to do is detect positives.

"Now, if you have a very positive compound, a very few animals—twenty, eighteen—will give you a positive result, but that means it is a very, very hot carcinogen. But I think that rather than specify the numbers, you can write the standard such, you know, you can pick up this much of a relative risk with this much of a 95 percent confidence limit. And I think that is the way to go." (Rall, Tr. 429)

Dr. McCann spoke of this, too:

"And in fact, false negatives in animal cancer tests is the biggest problem of animal cancer tests. This is because you can only do them with a limited number of animals.

"There are a number of examples of animal carcinogens that have been negative in one or two animal cancer tests and then positive in another. One of the most interesting examples is something called furyl furamide, or AF–2, that was used as a food preservative in Japan for about eight years. And they tested it in food, twice, in two animal cancer tests that were not horrible tests. They were fairly decent tests, and it was negative.

"After the eight years, Dr. Sugimura working in Japan, using a method very similar to ours, a bacterial test method, was starting to look at food, and he put a slice of fish sausage that happened to contain this preservative on a Petri dish and found a large number of revertant colonies coming up around the fish sausage, which indicated the fish sausage was mutagenic.

"He then started purifying the chemical from the fish sausage, thinking he was going to find a natural part of fish sausage mutagenic, and it turns out it was the food additive.

"That chemical was then put back into cancer tests, and they designed the test so that it was more complete. They used more animals. They did generally a more complete test, and it turned out positive. And it has been banned now. In fact, they withdrew all the food that contained it.

"But there are a number of examples of that, and I think in general, animal cancer tests are proving themselves to be—they are very good, in one sense. They are weakest, I think, in the area of detecting weaker carcinogens and in the area of false negatives." (McCann, Tr. 1585–1586)

An experiment with 100 animals would only be able to identify statistically a carcinogen of considerable strength. As Dr. Richard Bates (NIEHS; FDA) remarked:

"A study in 100 animals, a common size of experimental group at the present time, can obviously not detect anything lower than a one percent incidence of cancer. In actual practice, statistical considerations only permit the detection of a risk several fold larger than this for rare tumors and considerably larger if the types of tumors induced are those found with significant frequency in untreated control animals." (Bates, S. 13)

Dr. William Nicholson (Mt. Sinai School of Medicine) voiced this same concern:

"Current animal bioassay experiments really only select out the fairly strong carcinogens. We are dealing with 100 animals, and to see an effect there, you only would be able to do so with something that has significant potency. So if it does have an effect in animals, then it is of a strong enough nature as a carcinogen that one certainly should take heed with respect to human exposures." (Nicholson, Tr. 1714)

Sensitivity also involves a number of other aspects of the experimental protocol. Dr. Umberto Saffiotti (NCI) pointed out inadequate pathological examination as a possible source of false negatives:

"One (point) is what I call great limitation in the detectability of carcinogenic effects in these experimental groups. As we all know, the detectability is largely a function of the magnitude of the experimental group; is a function of the extent of observation; for example, the extent of pathology that you do on the animals on the test.

"If you sample a few tissues from a group of animals and only look at them microscopically, you may have tumors present in the tissues you are not processing and miss them. Equally, if animals die in an experiment and are not properly autopsied, they may have tumors that are not seen.

"Now, even in the best of experiments in which all the animals are carefully examined, the major limitation comes from the number available. So there is that limitation of the detectability of an effect." (Saffiotti, Tr. 855)

Dr. William Lijinsky (NCI–FCRC) discussed the balance that must be struck in selecting the appropriate dosage for an optimally meaningful experiment:

"For reasons again of statistics, we have to use as high a dose as we can because the exposure period is so much shorter than that which man might experience. And we want to produce as large an effect in that small group of animals as we can . . .

"What we have to guard against in a bioassay is a false negative. We do not want to conclude from an inadequate test that the compound is safe when it, in fact, is a carcinogen. So we want to use as high a dose as we can. However, we do not want to use a dose so high that it upsets the dynamics of the body in such a way that the animals die early, for example. The main reason that we do not—that we use a maximally tolerated dose and not the maximum dose is that we do not want the animals to die before the end of their normal lifespan, so that we are sure we give the greatest possible opportunity for tumors to develop. That is the reason we adopted a maximally tolerated dose, not a maximal dose. It has nothing to do with differences of metabolism." (Lijinsky, Tr. 1075–1076)

In his written testimony, Dr. Saffiotti stated that he did not feel the exposure regime of standard carcinogenesis tests achieves maximum possible sensitivity:

"The chronic treatment is started when the animals "should be no older than 6 weeks of age and, if possible, weanlings". This choice makes the test much less sensitive than those in which the test compound is administered to the parents of the test animals before conception and to the pregnant mothers through the gestation and nursing periods and to the test animals from their birth. Many chemicals induce a much more marked carcinogenic response when administered during the development of the organism, in the fetal or neonatal periods (Rice, 1976). Yet the current test standards do not require that all chemicals be tested under such conditions of high susceptibility. The animals are then exposed to the test treatment for a large portion of their lifetime. The NCI guidelines recommend 24 months of observation without treatment; the surviving animals are then sacrificed. Such a schedule falls short of providing a full lifetime exposure, particularly for rodent strains that may live up to 3 years. The sacrifice schedule may also cut short the appearances of late tumors or the further manifestation of invasion or metastases. The use of only 50 animals per group limits the detectability of effects to those appearing with a frequency near 1 in 10 or higher, clearly several orders of magnitude above those levels of risk (e.g., 1:10,000 or 1:100,000) that would represent serious hazards in people." (Saffiotti, S. 10–11)

Very few witnesses dissented from the general principle that animal tests are insensitive. However, a few witnesses argued that the inherent sensitivity of certain animal models may offset the statistical insensitivity of the experiments in which they are used. For example, Dr. Francis J. C. Roe (AIHC) made the following statement:

"It is sometimes suggested that man may be more sensitive than laboratory animals to the induction of cancer by a particular agent. This possibility certainly exists just as does the possibility that a particular agent that does not cause cancer in animals will do so in man. Either situation could arise, for instance because the metabolism of an agent in man is different from its metabolism in laboratory animals. However, by far the more likely situation is that laboratory animal test systems are *more* sensitive than man. I say this because of the greater likelihood that the laboratory animals used for tests will have

been selected for genetically-determined or virus-determined high sensitivity to tumor induction. Also, several aspects of the laboratory environment (e.g. over-feeding, abnormal hormonal status, see section 3) increase the risk of tumor development in response to non-specific factors." (Roe, S. 75)

However, there was no convincing testimony to suggest that the use of sensitive animal models would lead to "false positive" results. Indeed, available evidence is sufficient to discount such a suggestion (Tomatis, 1977a, p. 305). Thus at best these arguments would be relevant only to the issue of quantitative estimation of risks: they provide no basis for discarding positive results even in allegedly sensitive systems. Hence substantial evidence presented in the Record generally supports the proposition that animal experiments are insensitive, and that little weight, if any, can be placed on "non-positive" results.

There are two main types of situations in which OSHA might have to weigh "discrepant" results of animal testing:

(a) cases in which positive result(s) in one species has to be weighed against non-positive result(s) in other species;

(b) cases in which positive result(s) in one species has to be weighed against non-positive result(s) in the same species.

Case (a) has been discussed fully above. For the reasons given, it is concluded that in general, because of the varying susceptibility among animal species, positive results from testing in one animal species should always be given, in light of present scientific knowledge, greater weight than, and in fact supercedes, non-positive results obtained from testing in other species. The main issue to be discussed here is case (b), the weighing of positive and non-positive results obtained from testing in the same species of test animals.

A number of participants to this Rulemaking expressed concern, either in testimony or in briefs, that substances would be regulated on the basis of positive results in single tests, which might be of marginal quality, and that these results could not be outweighed by negative results, even if negative results were obtained in many tests. Examples of such comments are the following: Dr. Roy Albert (EPA), Tr. 2379–80; Council for Agricultural Science and Technology, S. 19; Hardwood Plywood Manufacturers Assoc., S. 2; Texaco, S.-Attachment 3. OSHA believes that such hypothetical cases are unlikely to arise in practice. In the first place, very few substances have been tested under adequate protocols with negative results more than 2 or 3 times. Indeed, no such case was presented during the hearings. However, if such a case were to arise, OSHA would review the data carefully and consider the possibility that the positive result might be a "false positive" (see subsection (d) below). Such a scientific review would take place as provided for in the final set of regulations. Secondly, OSHA does not in fact intend to regulate substances as Category I potential carcinogens on the basis of a single marginal positive result. OSHA will *ordinarily* require confirmation of positive results in more than 1 group of animals (see Section V.D. 9 below). Thus the sole remaining issue is whether *confirmed* positive results in one species should be superseded by non-positive results in the same species.

For comparisons within species, the same general principle applies: carcinogenesis bioassays are generally insensitive and little weight can be placed on non-positive results. Furthermore, there are differences in susceptibility within species which are liable to give rise to "false negative" results. This point was addressed by Dr. Umberto Saffiotti (NCI):

"As is the case with the variability among different species, so is it possible to observe a marked variability of response to a carcinogen among different strains of the same species. Therefore the intrinsic value of a positive response in a given strain—if technically valid—is not affected by the finding of positive or negative findings in other strains. The value of a positive result in a second strain simply provides further confirmation of the ability of the substance to exert a carcinogenic action. Another kind of confirmation may be obtained by the results of another experiment in the same strain. As with different species, there again the experimental conditions may vary from test to test and one does not necessarily have to expect that the carcinogenic response be qualitatively the same. The age at the time of exposure, the sex, the mode of administration, the dose and period of exposure, as well as dietary and maintenance conditions can affect the quality and intensity of the response in different experimental groups." (Saffiotti, S. 30–31)

* * * * *

"The tests are conducted usually only on two particular strains of animals, one strain of mice and one strain of rats. This extremely narrow range of biological variants represents another great limitation in the detectability of carcinogenic effects, which are often known to vary considerably in their intensity and localization among different strains and species. The observation of a tumor response only at very high doses in a given strain may be paralleled by the induction of a carcinogenic response detectable at much lower doses in another strain. An example of this variation of susceptibility is provided by the studies on the carcinogenicity of DDT. In strain Balb/c mice, only the dose of 250 ppm in the diet revealed a detectable carcinogenic effect, by observation in groups of approximately 120–130 female mice (Terracini, et al. 1973 a,b); in strain (C57BL/6xC3H/Anf)F1, positive results were found with a dose of 140 ppm, with initial exposures to 46.4 mg/kg b.w., from 7 to 28 days of age (Innes et al. 1969). In strain CF1— mice, however, a carcinogenic effect was detected down to levels of 2 ppm in the diet, well below the levels currently allowed as residues in several food products (Tomatis et al. 1972). This finding was subsequently confirmed." (Turusov et al. 1973) (Saffiotti, S. 11).

Dr. Benjamin Trump (Univ. of Md.) also commented on this point in regard to the use of inbred strains:

"The main problem, indeed, with inbred strains is that you might get false negatives, either because they are [not] sensitive or because of background, and so on." (Trump, Tr. 2014)

Hence, OSHA concludes that the proposition that positive results in general, should be given greater weight than non-positive results applies in the case of discrepant results within a single species. However, as pointed out below, OSHA believes that this issue should be reviewed in the "substance-by-substance" rulemaking and not foreclosed nor even limited. See 29 CFR 1910.143(d)

(d) *What precautions should be taken to avoid placing weight on "false positive" results?* Several witnesses emphasized that carcinogenesis bioassays, like all diagnostic tests, are liable at times to give both "false positive" and "false negative" results. Dr. Schneiderman (NCI) stated:

"How good are effectively diagnostic tests? Any of the short term tests, the animal tests and so on, are really diagnostic tests. We are trying to diagnose whether a particular material is a carcinogen or not, so in this sense they have all the characteristics of a diagnostic test.

"We are also trying to use 400 or 600 or 800 animals as a surrogate for a 100 million person labor force. The question then is: Do our diagnostic tests have—what kind of operating characteristics do they have? And the major operating characteristics that we know all diagnostic tests have * * * are that they have false positives and false negatives. And it seems to me that is the issue.

"I know of essentially no diagnostic test which is absolutely certain with respect to false positives and false negatives, and I think that is a characteristic of the testing that we are doing here." (Schneiderman, Tr. 311)

False positive results may arise in several ways: (a) from methodological errors in experimentation; (b) from confounding factors; or (c) from chance variations in tumor incidence. The first two types of errors can be minimized by applying good scientific judgment in

assessing the experimental results. Most of the legitimate concerns arise from statistical "false positives" of type (c).

Mr. Richard Peto (Oxford Univ.) discussed the statistical problems involved in analyzing experimental data on tumors at a number of different sites:

"Because in most experiments animals of both sexes and of more than one strain are studied, and the separate incidence of tumors at each of a dozen or more anatomical sites is independently documented, some of the many significance levels calculated will probably be less than 0.05 just by chance. Because of this, individual P-values of 0.05 (or even 0.01) are not necessarily convincing unless the effects concerned can be reproduced in independent experiments or unless the agents concerned show striking activity in a battery of short-term tests; for a single animal experiment to be convincing without such support, a P-value of well under 0.01 (perhaps even 0.001) should usually be required. Unless this policy of requiring rather extreme P-values is adopted, an unacceptably large number of misleading results will emerge by chance alone." (Peto, S. 17)

Dr. Joyce McCann (Univ. of Calif.) voiced a similar concern:

"The large number of tissues evaluated in a single cancer study can create false positives due to statistical fluctuation and unreproducible positive results can also be caused by unpredictable fluctuations in tumor incidence among control animals. For rare tumors, or in cases where a single test shows a positive dose-response result at more than one dose level, these statistical arguments do not as readily apply, and a "false positive" result is much more unlikely." (McCann, S. 24)

A number of other witnesses made essentially the same point (Council for Agricultural Science and Technology, S. 19).

One way to reduce the number of "false positives" is to apply a more stringent criterion for statistical significance before accepting a single positive result at one organ site. This procedure was proposed by Mr. Peto (S. 17, see above quotation). However, by requiring a higher degree of statistical significance, false positives are reduced at the expense of increasing the number of false negatives. Mr. Peto gave a specific illustration of this trade-off:

"Now, the trouble with taking a rather extreme definition of positive is that if something genuinely is carcinogenic but not very strongly so, as for example, saccharin, if you insist on a very extreme difference before you are convinced, then you will not be impressed by something which is a genuine carcinogen." (Peto, Tr. 2550)

This problem was analyzed by Fears *et al.* (1977) in an exhibit to the testimony of Dr. Griesemer (NCI). The authors showed that both false positive and false negative results are more likely at sites at which there is a substantial spontaneous incidence of tumors. Using data on spontaneous tumor rates in the NCI bioassay program, the authors calculated the probability of obtaining false positive results and false negative results under various methods of analyzing the experiment ("screening strategies"). Their principal conclusions were: (i) that any strategy to reduce the number of false positives results in an increase in false negatives; (ii) the probability of obtaining a false positive result is acceptably low if positive results are required at both doses in one site; (iii) the probability of obtaining false positive results is reduced still further by incorporating additional information. The following passage provides greater detail:

"The tissue site at which a significant result is found can be of considerable importance in a chemical screen. Tissue sites with high spontaneous tumor rates are more likely to yield false-positive results than are sites with low spontaneous tumor rates. For example, in the pituitary gland of the female Fischer 344 rat, the probability of a false positive in either of 2 dose groups is 0.059 and the probability of a false positive at both dose groups is 0.007. In contrast, for the majority of tissue sites (those with spontaneous tumor rates of less than 1%), the probability of a false positive in either of 2 dose groups is 0.00018. Thus, a significant result (even at only 1 dose) at a tissue site with a low spontaneous tumor rate offers strong evidence against the chemical under study. The presence of a dose-response relationship (higher tumor rates at higher doses) provides corroborative evidence of tumorigencity.

"The upper bounds on the misclassification rates for the decision rules considered in this paper offer valuable insight into the problems of chemical screening. The upper bounds for the strategy that indicates a positive compound if a significant result is found in either dose should serve as a warning against a screen that relies solely upon statistical significance and does not require biological consistency. The complex 2-species, 2-sex screen described previously which requires the supporting evidence of significance in both dose levels yields an acceptable false-positive probability. This lower false-positive error rate is accompanied by a higher probability of a false-negative result. Of course, there are other biologically consistent results that should be considered as evidence of tumorigenicity, such as the occurrence of a significant result in 1 dose for both male mice and male rats at the same tissue site. A good screen must incorporate biological knowledge and careful statistical analysis." (Fears et al., 1977 p. 1944; Exhibit to Griesemer Statement)

Dr. Bo Holmberg (Swedish NBOSH) commented on these results:

"It is however not very probable that a false positive result will be obtained (Page, 1977; Fears et al., 1977) even in a single animal test, should it be well performed. If a false positive result appears it does so only in remote cases and when high incidences of spontaneous tumors appear in the control series." (Holmberg, S. 26)

OSHA also is impressed by testimony that false negatives are of greater public health concern than false positives, and that an appropriate balance should be struck on this basis:

"I personally do not consider a few false positive results as being an important problem. I am generally more concerned with the false negatives, especially considering the inherent insensitivity of the conventional animal test systems." (Holmberg, S. 26–27)

Dr. Curtis Harris (NCI) stated that these were his priorities also:

"And I am frankly not very concerned about false positives. I am much more concerned about false negatives from a public health standpoint." (Harris, Tr. 2015)

OSHA concludes, on the basis of the above cited testimony and the other substantial evidence in the Record, that, if an experiment is analyzed properly ("incorporating biological knowledge and careful statistical analysis"), false positives are probably not of significant concern. The principal concern remains the likelihood of falsely *rejecting* positive results through taking precautions to minimize the possibility of accepting false positives.

(e) *How should OSHA deal with data of varying quality?* A final question raised in this rulemaking is how positive results obtained in experiments of poor quality should be weighed against non-positive results obtained in experiments of better quality. This question was posed, for example, in AIHC's Post-hearing Brief:

"OSHA's statement as to positive and negative results is stated in terms of tests of equal soundness from an experimental point of view. *Id.* There is, however, a general recognition that tests are of varying quality and, as many witnesses pointed out (*e.g.*, Dr. Griesemer, Tr. 930; Dr. Furst, Tr. 6924–6926, 7159–7160), the tests in the literature are recognized to be of very uneven quality. See discussion *supra*, at 128–131. Thus, OSHA's administrative determination is based on an assumption as to validity which is essentially unrealistic." (AIHC, Post-hearing Brief, p. 158; Hearing Exhibit 251)"

The Council for Agricultural Science and Technology (S. 19) also discussed this issue. Dr. Roy Albert (EPA) posed the problem in quite specific terms:

"If you have a marginally positive result in one study, then a series of negative studies provides evidence that weakens the strength of the evidence of its positivity.

"Now, if you say if you have one marginally positive study and one negative study how much does that reduce the weight

of evidence, or two negative studies and one marginally positive, or three negative and one—it is very difficult to say that. I must say that this is a problem of no small magnitude, because it is not out of the question, and the situation has arisen where economically important agents have one study done on them and they show up with a marginally positive result, and the question comes up, well, what do we do now? You know, there are people that are interested in using the material. You know darn well that if they go to the expense, and it is a very considerable expense, of doing another study and it turns out negative, the question is how many negatives does it take to wipe out that positive study? So I think this is a difficult situation, and I think it is clearest, as I said, when one has a marginally positive result and a series of negative results. This puts it in a category of a very weak response." (Albert, Tr. 2379–2380).

It should be noted that Dr. Albert was discussing in this passage the problem of evaluating a *single* test that was marginally positive.

Several witnesses argued that in evaluating the results of animal tests, it is appropriate to apply more stringent criteria to experiments which give non-positive results than to those which give positive results (Lijinsky, Tr. 1080; Epstein, Tr. 1462–1463). For the reasons given above, OSHA regards these arguments as reasonable. However, as discussed elsewhere in this Preamble, it is not scientifically justified to establish rigid criteria for the assessment of the "quality" of tests. If cases should arise in which data of varying quality need to be evaluated in light of each other, OSHA intends to rely on good scientific judgment to do so. However, such cases are unlikely to occur frequently, because OSHA will not ordinarily regulate substances as Category I potential carcinogens on the basis of single positive results. (See Section V.D. 9 on *Confirmation of Results).* Hence OSHA would not consider regulating a substance as a Category I potential carcinogen on the basis of a single test of poor quality. Finally, as Dr. Donald Kennedy (Commissioner, FDA) pointed out in the passage quoted above, experiments of poor quality are much more likely to lead to false negative results then false positives (Kennedy, Tr. 571–572).

c. OSHA's Conclusions

At the outset, it was noted that the issue of "non-positive" evidence, derived from the human or test animal experience, generally arises in three different contexts, namely: (1) positive animal data and "non-positive" human data; (2) positive test animal data in one species and "non-positive" data in another species of test animals; and (3) positive test animal data in one species and "non-positive" data in the same species from other testing.

(1) This first scenario was fully discussed above under Section IV, above. To recap however, OSHA concluded in section IV that the limited sensitivity of the epidemiologic method required that, except in the confines of certain narrow exceptions to the general policy, as provided, the results of a positive study or studies in humans or animals supersede or outweigh any "non-positive" study or studies in humans. Few such "non-positive" studies are available, as discussed, that can reliably detect less than a 50% increased incidence of cancer at any potential target site for workers exposed for the majority of their working lives. If such a study on a substance subject to rulemaking is made available to OSHA, it will be responsibly considered by the Secretary, as pointed out.

(2) The second scenario that arises from positive results from testing in one species of test animals and "non-positive" results from testing in another test animal species is discussed above under subsection 6(2)(c). There, we concluded that, because of the limited sensitivity of tests in experimental animals and because different species of animals vary in their susceptibility, positive results in one species supersede or should be given greater weight than "non-positive" results from testing in another species, in establishing the qualitative inference of carcinogenic hazard to workers.

(3) Based on the discussion of the evidence in the Record above, OSHA concludes here that when positive and non-positive results are reported in the same species of test animal, positive results in studies providing biological and statistical evidence of acceptable quality should be given the greater weight. This is particularly true in light of the limited sensitivity of testing in experimental animals. Nevertheless, because of the stated need for scientific flexibility, as discussed below, OSHA has provied for a mechanism to additionally consider such evidence discounting positive results, under unusual circumstances as specified in sections V.D. 3, 8 and 13 below.

Thus to reflect OSHA's intent as to the last two possible scenarios, the OSHA Cancer Policy provides (1990.143(d)):

(d) *Non-positive animal studies.* Positive results in one or more mammalian studies will be used for the qualitative identification of potential occupational carcinogens, even where non-positive studies exist in other mammalian species. Where non-positive and positive results exist in studies in the same species, the non-positive results will be evaluated.

3. Testing at High Doses

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA proposed to rely upon positive results from experiments in laboratory animals conducted "at any level of exposure or dose". The basic rationale supporting the proposal was the necessity to evaluate the biological effects of a substance under test all the way to the highest levels of exposure compatible with lack of unrelated toxic effects, and, in addition, to overcome the statistical insensitivity of laboratory bioassays conducted with the limited numbers of test animals that could be handled in practical laboratory conditions. Stated a different way, OSHA believed that laboratory bioassays conducted at doses and under experimental conditions likely to yield maximum tumor incidence were valid qualitative indicators of carcinogenic hazards, and that such testing should indeed be encouraged because it gives more reliable qualitative results than testing at lower doses.

b. The Public's Response and OSHA's Evaluation

Virtually all of the witnesses and participants addressing this issue endorsed the propriety of testing at levels higher than those levels to which humans are actually exposed. Nevertheless, there was some debate as to the actual magnitude of the levels of exposure that can be used in carcinogenicity tests without impairing the reliability of such testing as predictors of carcinogenic hazard or risk. And there was also some concern raised as to the use of such doses as used *in practice.*

For the purposes of the following discussion, it should be pointed out that, in general, the term maximum tolerated dose (MTD) is usually defined as the highest dose of a substance under test, given during a chronic study, that can be predicted not to alter the treated animals' normal longevity from toxic effects other than carcinogenicity. Since the determination of an MTD is judgmental in nature and often based upon subchronic data, the judgment may be wrong. As Dr. Leon Golberg of the Chemical Industry Institute of Technology (CIIT) pointed out: "[E]very' one of us is liable to err in reaching a [MTD] decision." (Golberg, S. 3). Thus, although the proposal by OSHA and, understandably, all witnesses referred to a maximum tolerated dose or "MTD", OSHA believes that the term *estimated*

maximum tolerated dose or "EMTD" may be a more accurate description of the state of the scientific art than the term "MTD". Thus EMTD will be used throughout this preamble.

Three principal issues were raised in this proceeding concerning the issue of EMTDs:

1. Is it generally appropriate to test laboratory animals at the highest dose level that can be tolerated by them during lifetime administration (the EMTD) to determine qualitatively a carcinogenic hazard?
2. Are there biological reasons to believe that substances tested at high doses will produce carcinogenic effects at the highest dose but not at the lower doses?
3. How is the EMTD to be defined and should the results of experiments in which the EMTD is exceeded be discarded?

1. *The General Appropriateness of EMTDs.* A great many witnesses supported the use of an EMTD for qualitative identification of carcinogenic hazards. Dr. Arthur Upton (Director, NCI) stated in his direct testimony:

"To offset the statistical insensitivity as much as possible, it has become standard practice to test chemicals for carcinogenicity at relatively high doses. This practice has been endorsed by almost all workers in the field, including the expert international and national committees cited above. In the NCI bioassay two doses have usually been used—the maximum tolerated dose (MTD) and one-half of the MTD. Probably no feature of carcinogenesis bioassays is so widely misunderstood or misrepresented as the use of these relatively high doses. Contrary to widespread popular belief, there is no evidence that a chemical which is carcinogenic at high doses would not also be carcinogenic at lower doses. The evidence, in fact, is that it is likely to be carcinogenic at any dose, but at a frequency which is much less likely to be detectable at low doses than at high doses. Criticism of high dosages used in animal tests may be based on a misunderstanding of their purpose. The tests are intended as screening procedures, to identify those chemicals with the potential to cause cancer, not as tests to measure the frequency of induced cancer at a particular level of exposure." (Upton, S. 11)

Dr. Richard Griesemer (NCI) in his direct testimony stated:

"When the objective of the experiment is to determine the capability of the chemical to produce cancer, it is mandatory that experiments in animals be conducted with large doses. The general approach recommended by NCI is to select the highest dose of the test agent that can be predicted not to alter the animals' normal longevity from effects other than carcinogenicity. If this approach is not used or if chemicals are not tested under the most rigorous conditions, then negative results are meaningless. (Griesemer, S. 6, footnotes omitted)

Dr. Griesemer (NCI) during his cross-examination commented further:

"I believe strongly that if one does not pursue the testing of chemicals for carcinogenicity at the maximal *tolerated* dose, that one runs the risk of missing carcinogens. I find it hard to believe that there are non-carcinogens which when given in excessive doses will produce cancer." (Griesemer, Tr. 997–98)

Dr. Umberto Saffiotti (NCI), testifying with Dr. Griesemer, agreed:

"I . . . also do not really find any scientific basis presented to justify the selection of these levels as those . . . above which it is not useful to study the effect of certain chemicals. (Saffiotti, Tr. 998)

Dr. Saffiotti (NCI) in his direct testimony expanded upon this issue, *viz*:

". . . there is a broad consensus of qualified scientific opinion that carcinogenesis tests should include bioassays at or near the highest tolerated dose level. If a substance had only been tested at lower level and no carcinogenic effects had been detected, this would only tell us—as is always the case with negative results—that the effect in the chosen test system was below the detectability threshold of that particular test. We would be left totally uninformed as to whether a detectable response may be induced by the test compound at higher levels of administration. Which maximum test dose-level should then be chosen? Any level other than the MTD would not represent a maximal challenge of the chosen test system, and might be expected to yield a correspondingly lower response, unless the test system were changed to a more sensitive one, either by increasing the number of test animals proportionally or by switching to a more sensitive biological model. To increase the number of test animals adequately, as required in order to extend detectability of effects to lower doses, might create extremely serious logistic and economic problems. The adoption of test systems more sensitive than those currently recommended for standard testing is an alternative possibility that could be given further consideration. Presently accepted bioassay standards, such as the NCI "Guidelines for Carcinogen Bioassay in Small Rodents" (Sontag, Page, and Saffiotti, 1976) are far from recommending extreme conditions of test. Adoption of standardized test protocols always implies acceptance of some arbitrary selections, which should be made on the basis of best judgment by highly knowledgeable experts." (Saffiotti, S. 8–9)

Dr. William Lijinsky (NCI–FCRC) in his direct testimony expanded upon the issue:

"The dose chosen (for testing) is usually the maximally tolerated dose (MTD), that is, the highest dose which can be given for a prolonged period without causing detectable toxic effects in the animals, as detected by weight loss and by pathologic examination.

"The reason for using the maximally tolerated dose, rather than a lower dose more closely resembling the quantities to which people might be exposed, lies in the numerology of carcinogenesis. We accept a number of premises which are based on our experience of carcinogenesis studies. These are that carcinogenic effects are cumulative, that individual responses to carcinogens vary over a range, that man is no more sensitive than the animals to the action of the carcinogen, and that there is a relation between dose and tumor response which reveals itself as an increase of incidence of tumors and a decrease in the time taken to develop tumors as the dose increases, and vice-versa.

"Let us assume that 100,000 people will be exposed to the substance for a considerable portion of their lifetime, and that 100 of them, or 1 in 1,000, will develop tumors from the exposure (in the case of a substance used as a food additive to which millions of people are exposed, the numbers would be increased proportionately). In order to detect this risk in a group of animals of manageable size the dose must be increased greatly, because the induction of 1 tumor in 1,000 animals would require a group of at least 1,000 test animals, clearly an unwieldy number. Unfortunately, one tumor of a certain type induced in a group of animals of any size is not statistically significant, since it could occur by chance. Even 2 or 3 could occur by chance. In practice, the minimum number of cases which is considered significant is 5. Therefore, strict numerical equivalence with the human experience would require a group of 5,000 test animals in which 5 tumors of a certain type would be found, none of which occurred in a group of 5,000 untreated controls. This is a requirement for 10,000 animals for a test of one substance at one dose in one sex of one species. Clearly the cost would be outrageous and there would be the possibility of having selected an unsusceptible species or sex. Even under these conditions the dose given to the animals would have to be increased at least 30 times over that to which people are exposed to compensate for the differences in exposure times.

"To make the test more manageable than that described we use groups of 50 males and females of each sex of two species and give such groups one or two doses of the substance for their lifetime. We increase the dose as much as possible below toxic levels (at least 30–100 times above human doses) and in practice use the MTD. We then look for an incidence of at least 5 animals with an induced tumor which does not appear in the controls before it is considered that the substance is a carcinogen. However, it is only necessary to find such an incidence in one of those groups for the test to be positive, as explained above. On the other hand, if there is no significant incidence of induced tumors, we can say that the substance is non-carcinogenic and 'safe' although all we have shown is that fewer than 1 in 1,000 people exposed to the substance will develop cancer. It is not possible to extrapolate risk from such an experiment since the conditions of the test are so coarse. We have not considered the possible synergistic action of other carcinogens, as man might be exposed to. The possible effects of promotors, or of antagonists, have not been considered. At best the test, if positive, tells us that there is a risk. If we were to be conservative and include the possibility that man is more

sensitive than the experimental animals to the carcinogen, then the factors discussed above might not be adequate and larger groups of animals should be employed anyway, but this is probably not feasible." (Lijinsky, S. 27–30)

Dr. Lijinsky, during his cross examination, commented further:

"It is not adequate to test chemicals at the low doses to which man is exposed, since even those chemicals known to be carcinogens in man will give false negative results under these conditions. This is because of the shorter exposure time of the experimental animals, only two years, compared with man's lifetime, which is 50 years or more, and to the smallness of the group of animals, 50 or 100 usually, compared with the human population at risk which might be millions, of which some might be much more susceptible than others. In no case is the mechanism of action of any carcinogen known in man or animals, so comparisons of metabolism cannot be assumed to indicate that man is more or less likely than the animal to be susceptible to the risk of cancer in exposure to a carcinogen." (Lijinsky, Tr. 1020)

Dr. Lijinsky again emphasized later in his oral testimony:

"For reasons again of statistics, we have to use as high a dose as we can because the exposure period is so much shorter than that which man might experience. And we want to produce as large an effect in that small group of animals as we can so that we safeguard the population." (Lijinsky, Tr. 1075)

Dr. Lorenzo Tomatis (IARC) also noted in an article attached to his written statement:

"The choice of a sensitive model appears to be justified as an attempt to compensate for the limited number of animals normally used. One of the reasons given for underestimating or disregarding animal experimentation is that results are often obtained by the second approach, that is, by using a model which is accused of being too sensitive. There is sufficient evidence to indicate that experimental results can indeed predict a hazard to man (Tomatis, 1974; Tomatis et al., 1973), while there is no evidence that, for instance, a chemical which is carcinogenic to experimental animals will not in any circumstances produce tumors in man." (Tomatis, 1977, p. 305; Appendix 3 to Tomatis Statement)

Dr. Harold Stewart (NCI) introduced a report addressed to the Director of NCI by an Ad Hoc Committee on Testing for Environmental Chemical Carcinogens, which included the following passage:

"There can be no question of the value of investigating carcinogenicity at different dose levels of the agent. For example, information as to mechanisms of action and the influence of modifying factors might be better obtained with minimally effective than with maximally tolerated amounts. However, this is not relevant to *identification of environmental carcinogens and assessment of their significance for human cancer,* which are our immediate concerns. Moreover, in the case of many, if not most, carcinogens, decreasing the dosage from a maximally effective to a minimally effective level produces prolongation of the latent period in addition to decreased incidence of tumors. If the dose is lowered to a point at which the mean latent period exceeds the life span of the animal, negative results may be obtained at levels that might be carcinogenic for equally susceptible, longer-lived animals." (Stewart, S. 3, emphasis added)

Dr. Richard Bates (NIEHS, FDA) testified:

"Animal experiments are usually conducted at considerably higher levels of exposure than those customarily occurring in humans, though in some poorly controlled occupational settings it is possible for workers to be exposed to high levels of carcinogenic chemicals. Since this practice of testing at high dose levels is often challenged, some comments about it are in order. The fundamental reason for doing so is to enhance the sensitivity of the experimental bioassay to detect a chemical carcinogen. A study in 100 animals, a common size of experimental group at the present time, can obviously not detect anything lower than a one percent incidence in cancer. In actual practice, statistical considerations only permit the detection of a risk several fold larger than this for rare tumors and considerably larger if the types of tumors induced are those found with significant frequency in untreated control animals. This level of risk is considered much higher than that which is socially acceptable in an exposed human population. In order to detect lower levels of risk, it is either necessary to test in much larger groups of animals or to test at much higher dosage levels than those to which humans are exposed and use mathematical procedures to estimate the level of risk from lower levels of exposure." (Bates, S. 12–13)

Dr. Bernard Weinstein (Columbia Univ.) testified:

"It would, of course, be desirable to expose test animals to doses which are within the range of human exposures. However, this is not feasible for a number of reasons. First, the animal assay system is relatively insensitive because of the limited number of animals that can be used in a specific study. If only 50 to 100 animals are used, then the system would be sensitive at only about the 10% level; that is, about 10% of the animals would have to get tumors for such an effect to be considered statistically significant. It would require an extremely potent carcinogen to produce 10% tumors if the agent were given at low doses; so the conventional procedure is to increase the dose to increase the tumor yield if the compound is indeed carcinogenic." (Weinstein, S. 4)

Dr. Renate Kimbrough (CDC) commented in her oral testimony:

"You would not want to do a cancer study and give doses that are so high that you lose most of the animals before they ever come to the point where most of them would develop cancer. And on the other hand, you do not want to make the dose so low that because you are dealing with a small group of animals, you could miss the fact that the compound is a carcinogen. So what you then arrive at is the tolerated—the highest tolerated dose and you would have to use those dosage levels because of the small number of animals that you are exposing. In other words, your system that you are using, the animal system, is not very sensitive, the way we are doing the studies at the moment. Therefore, you try to use the highest tolerated dose and do your study with that, even though you know that people often are exposed to less, since we are trying to protect people that are exposed in much larger numbers and that also have—they have genetic differences to the susceptibility that might be differently affected by the carcinogen. In order to try to cover all of that, we should have a fairly high dose." (Tr. 1788–89)

Dr. Benjamin Trump (Univ. of Md.) commented during oral testimony why testing at the EMTD is appropriate:

". . . to try to get around the relative insensitivity of the assay. Animals only live for two years. If lower doses are done you get to the background level, and this is one of the reasons for the insensitivity, because even something that causes an event one in ten thousand times in humans would be a significant number of cancers. So it would not even be satisfactory at that level. So to get around all those problems, to get around the short lifetime of the rodents, it is necessary to use high doses, and this to me is very logical." (Trump, Tr. 2008)

Other witnesses who supported the use of testing at the EMTD included: Dr. Donald Millar (Acting Director, NIOSH), Appendix C to NIOSH statement, p. 15; Dr. William Nicholson (Mt. Sinai School of Medicine), S. 2; Dr. David Rall (Director, NIEHS), S. 8; and Mr. Steven Jellinek and Dr. Roy Albert in their joint statement for EPA, S. 2.

A principal purpose of using the EMTD is to maximize the sensitivity of a bioassay. Dr. Richard Griesemer (NCI) discussed this in his oral testimony:

"Again, if the purpose of the study is only to determine whether the chemical is capable of producing cancer in animals, then it is desirable that the experiment be conducted under the most rigorous conditions for producing that result. That is, one would use as many animals as possible, he would use as many routes as possible, he would use the largest doses that are compatible with a long lifetime so that the animal has time to develop cancer, and to that extent the general principles of toxicology apply." (Griesemer, Tr. 936)

Dr. Lijinsky (NCI–FCRC) testified similarily:

"As I said, what we have to guard against in a bioassay is a false negative. We do not want to conclude from an inadequate test that the compund is safe when it, in fact, is a carcinogen." (Lijinsky, Tr. 1076)

Other scientific and regulatory bodies have, in the past, supported the same position proposed by OSHA. As the NCI Ad Hoc Committee's report to the Surgeon General stated:

". . . bioassay methods have remained tools of low sensitivity, capable only of detecting the highest peaks of carcinogenic activity. The factor which limits bioassays sensitivity is usually the small number of test animals used. If the bioassay design has a low probability of detecting carcinogenic effects produced by hazards at levels comparable to those present in environmental samples, then tests at such levels are wastes of time, effort and money. The need to test levels higher than those found in the environment is thus founded. (NCI Ad Hoc Committee, 1970, p. 7)

In 1973, the Canadian Report on Protocols For Testing of Chemicals For Carcinogenicity stated:

"Selection of doses to be tested is currently a subject of controversy, particularly in relation to food additives and certain environmental chemicals. In carcinogenesis testing, the highest dose level should be within the toxic range, but should be consistent with the prolonged survival of the majority of animals. The lower levels should permit the animals to survive in good health for their natural life span or until tumors develop (WHO, 1969). Use of very high dose levels has been critized [*sic*] on the basis that it can be incompatible with normal physiological function and creates a metabolic overload on the animal. Higher doses are sometimes selected to delineate mechanism of action and metabolism of carcinogens but there is some question as to whether data obtained from such studies is representative of the situation at lower dose levels (Weil, 1972). Most investigators have used at least three dose levels which is compatible with WHO recommendations on food additives and drug carcinogenicity testing and is in keeping with Canadian guidelines on testing of food additives. It is generally intended that the lowest dose selected will produce no real increase in tumor incidence over control animals." (Health and Welfare, Canada, 1973, p. 19)

In 1975, the National Academy of Sciences in *Contemporary Pest Control Practices and Prospects* stated at p. 65:

"The sensitivity of such tests is inherently limited by the number of animals employed. For example, even if no cancers are found in a group of, say 100 animals, one can conclude with 95 percent confidence only that the true frequency of cancer induction at the given dose is less than 3 percent. Clearly, in extrapolation to man, a likelihood of inducing cancer in no more than 3 out of 100 individuals would hardly be reassuring. In practice, animal tests may be even less sensitive than the foregoing example suggests. This is because the control animals themselves may develop a substantial frequency of various kinds of cancer, making the problem one of detecting a significant increase above an already appreciable background. In order to increase the sensitivity of animal tests, administered doses are chosen to be considerably higher than the level to which humans usually are exposed. This procedure may fail if the test compound greatly shortens the life span of the animals as a result of toxic effects other than cancer. In that case, the older ages at which carcinogenesis is likely to be most manifest cannot be studied." (NAS, 1975a, p. 65; Appendix H to Rall Statement)

In 1977, in *Drinking Water and Health*, the National Academy, in summarizing its discussion of "Chemical Contaminants: Safety and Risk Assessment" stated:

"The exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in man.

"The most commonly expressed objection to regulatory decisions based on carcinogenesis observed in animal experiments is that the high dosages to which animals are exposed have no relevance in assessment of human risks. It is therefore important to clarify this crucial issue. Practical considerations in the design of experimental model systems require that the number of animals used in experiments on long-term exposure to toxic materials will always be small, compared with the size of the human populations similarly at risk. To obtain statistically valid results from such small groups of animals requires the use of relatively large doses so that effects will occur frequently enough to be detected. For example, an incidence as low as 0.01% would represent 20,000 people in a total population of 200 million and would be considered unacceptably high, even if benefits were sizable. To detect such a low incidence in experimental animals directly would require hundreds of thousands of animals. For this reason, we have no choice but to give large doses to relatively small experimental groups and then to use biologically reasonable models in extrapolating the results to estimate risk at low doses." (NAS, 1977a, p. 55; Appendix I to Rall Statement)

And in *Cancer Testing Technology and Saccharin*, the Congress's Office of Technology Assessment stated that:

"Standard procedure in animal cancer tests is to feed substances at the 'maximum tolerated dose'. . . . Contrary to popular opinion, all chemicals do not cause cancer at high dose levels. Many food additives and other chemicals have been tested in animals at this level without causing cancer.

"The rationale for feeding large doses of a substance in animal tests is as follows. As the dose of a substance that causes cancer is increased the number of exposed animals that develop cancer also increases. To conduct a valid experiment at high dose levels, only a small number of animals (perhaps several hundred) is required. However, to conduct a valid experiment at low dose levels, a very large number of animals is required. (The smallest incidence rate detectable with 10 animals is 10 percent or one animal. To detect a 1-percent incidence rate, several hundred animals would be required.)" (OTA, 1977, pp. 11–12. Exhibit C to Weinstein Statement)

And on February 1, 1979, the Office of Science and Technology Policy of the Executive Office of the President stated in a staff paper, *Identification, Characterization, and Control of Potential Human Carcinogens: A Framework For Federal Decision-Making:*

"High dose testing is a necessary feature of laboratory bioassays, given the limitations of time and study animals. The finding of cancer in animals only at high doses does not imply that such doses would be required in humans—particularly in view of the longer exposure periods existing in the human case. Animal dose levels should, however, be selected so as not to induce overt toxicity unrelated to carcinogenicity. Toxic doses may result in the dysfunction of metabolic processes that at lower levels might protect the animal (and humans) from cancer." (OSTP, 1979, p. 9)

These points have also been expressed in precedents established by the Administrator of EPA, who stated in *In re Shell, supra:*

"High doses are administered in animal tests, not because the researchers seek to correlate animal response levels to humans, but because with a limited number of animals this methodology is necessary to determine gross effect. Consequently, a substance that will induce cancer in experimental animals at *any* dose level, no matter how high or low, should be treated with great caution." (footnotes omitted). (39 FR 37268)

Again, in *In Re Velsicol*, EPA addressed this issue and stated:

". . . High doses in animal experiments are thus justified, and indeed necessary, because the comparatively small numbers of animals necessarily involved in the experiments make it very difficult at least to test for positive results at lower doses.

"Testing at . . . relatively high doses is now generally regarded as essential to the attempt to reduce the gross insensitivity imposed on tests by the small size of animal groups routinely tested, such as 50 or so rats or mice per dose level per chemical, compared with the millions of humans at presumptive risk . . ." (41 FR 7575)

FDA has also said, in eliminating chloroform from drugs and cosmetics (41 FR 26842):

"b. The comment also argues that the dosage in the NCI studies was excessive and thus does not support the contention of risk to humans. Noting that the NCI report stated that the methodology used in their studies differs from that which is currently used by NCI, the comment states that the most serious defects in the methodology used are the inadequacy of the subchronic toxicity study to determine the maximal tolerated dose (MTD) and one-half MTD, and the failure to employ a meaningful definition of MTD. The comment further states that had a proper and reliable subchronic study been

conducted, employing liver and renal function measurements as well as histological assessment of the effects of chloroform upon the liver and kidney, it would have been found that the dose levels used were too toxic. In support, the comment notes that in the NCI rat study, the dose levels had to be reduced after 22 weeks of treatment because the lethal consequences were too great. The comment also cites in support a short term study conducted at Bio/dynamics Inc. at dosage levels of 60, 120, 240, and 480 milligrams/kilogram and with the same strain of mice as that used in the NCI study. In the Bio/dynamics Inc. study both males and females had poor tolerance to the chloroform and at the 480 and 240 miligrams/kilogram levels most of the mice died.

"It is the Commissioner's opinion that the growth and survival curves as plotted for the mice in the NCI report reveal no significant effect on growth from the dosages administered, and only in the high-dose level female mice is there an effect seen on survival. However, this effect was observed late in the study, when the death rate showed a sudden increase after the 70th week. The Commissioner therefore concludes that the dosages in the NCI mouse study conform to the standard generally accepted for an MTD to be used in carcinogenicity studies.

"In the NCI rat study, it is true that the survival rate for chloroform-treated rats was lower than that for control rats.

"However, in the Commissioner's view the high dosage level for male rats appears to conform to standards for MTD when the first 90 days of the growth curves are examined. The comment's objection regarding excessive dosage (greater than MTD) would apply only to female rats. In this regard the Commissioner notes that the statement in the comment that dosage levels employed had to be reduced after 22 weeks because of lethality applies only to the female rats. Despite the reduction in dosage, the survival curves show a consistently lower survival rate. However, the Commissioner emphasizes that there was no increase in tumors reported for these animals. Rather, it was only in the male rats that an increased incidence of renal tumors was reported.

"The comment also points out that the ratio of tumor-bearing animals to animals involved in all chloroform treatment groups is less than that found in both male and female matched control groups. This observation, however, is noted and described by NCI in their report as not significant. Moreover, the Commissioner believes the distribution of other than kidney tumors to be normal. Aside from this, the comment disregards the dose-related time of tumor onset. The CTFA analysis further states that "* * * data for the female groups indicate that chloroform treatment may have actually exerted beneficial effects." Obviously, the lethal effects cannot be viewed as beneficial. Finally, the Commissioner notes that in the case of male rats where dosage would appear to conform to the generally accepted standard for carcinogenicity studies, definite evidence of kidney carcinogenicity appeared." (41 FR 26842)

2. Do Biological Reasons Make Testing at EMTDs Inappropriate?

Some witnesses, who objected to OSHA's proposed reliance on experiments which utilize the EMTD, proposed mechanisms by which chemicals might hypothetically show carcinogenic effects only at high doses. Some of these witnesses argued that any chemical, if given at a high enough dose, may produce cancer due to metabolic overloading of the body's natural detoxification mechanisms. Specifically, some witnesses proposed that with some sufficiently high dose there is a discontinuity or shift in the dose-response curve resulting in metabolic and pharmacokinetic factors which would lead to carcinogenic effects only at doses above the discontinuity.*

Dr. Perry Gehring (Dow Chemical) was a major witness supporting the hypothesis of "metabolic overloading":

"Because of the biochemical mechanisms involved in the genesis of cancer it is *scientifically reasonable* to conclude that administration of large doses of chemicals to animals for cancer testing assesses improperly the risk of exposure to low doses." (Gehring, S. 3, emphasis added)

He went on to say:

"Only relatively high doses can, in practice, yield statistically significant data. But *frequently* such high doses produce cancer simply because their very immensity overwhelms the biochemical pathways that would detoxify smaller, more realistic doses." (Gehring, S. 13, emphasis added)

* * * * *

"Dose-response curves may show an unusually large increase in response with increasing dose, starting at the dose level where "saturation" effects become evident . . . The overwhelming of detoxification processes is particularly important in carcinogenesis because reactive electrophilic intermediates will react with macromolecules such as DNA, rather than being detoxified." (Gehring, S. 17)

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. . . it is clear that as dose increases there is a disproportionate increase in the amount of reactive metabolite bound to genetic material escaping repair . . . The formation of such material is probably associated with chemical carcinogenesis . . . data generated from studies of animals given large doses cannot be extrapolated to predict the incidence of cancer caused by exposure to smaller amounts of the same chemical. Such extrapolation assumes that the fate of the chemical does not change with dose—an assumption which requires the curve of unrepaired "damaged" genetic material to be a straight line parallel to the abscissa. Clearly it is not." (Gehring, S. 19)

Dr. Benjamin Van Duuren (New York Univ.) also commented on this issue:

". . . there is a process that is called metabolic overload, and that if one gives a very weak carcinogen or a non-carcinogen in an extremely high dose, you might cause changes in the metabolism, the enzymatic activation and deactivation of the chemical, so that what would really normally be in the workplace, a non-carcinogenic chemical, may give rise to cancer, yes." (Tr. 1876)

Dr. Carroll Weil (Carnegie Mellon Univ.) also claimed that metabolic differences could be important:

". . . massive doses can result in different metabolism and pharmacokinetics than do concentrations similar to the one [sic] to which man will be exposed. (Tr. 6594–95)

Dr. Paul Kotin (Johns-Manville) also commented on testing at high doses:

". . . my concern over the high dose is that if it becomes shown that the high dose doesn't utilize certain detoxification mechanisms, whether it is conjugation or whether it is chewing up of certain amino acids, like glutathione or the like, then again the objection becomes meaningless in the sense that the high dose and the low dose have an anatomic and metabolic fate independent of the size of the dose." (Tr. 8716)

Dr. Kotin proposed still another problem with testing at high doses:

". . . the high doses interfere with repair mechanisms, and I am not limiting it to the repair mechanisms associated with DNA repair and so on. I am speaking about the ability of a macromolecule to heal itself or to have a cell organelle—let me put it that way—interfered with, even lysed within the cell by an exogenous agent at a given dose might be very much meaningless in terms of the preponderance of organelles there to keep the cell in a state of homeostasis or equilibrium.

"A large dose can result in the lysis of the cell if you get enough lysosomes strewn out within the cell, as the result of an overwhelming dose of an agent.

"At the level of metabolic pathways I have mentioned, the availability of buffering macromolecules like amino acids that serve

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* The following is a list of some of the participants who expressed support of the above arguments, especially the comment that OSHA was not considering evidence that detoxification mechanisms may be overwhelmed at high doses (i.e., EMTD levels): Dr. Marvin Friedman (Allied Chemical) (S. 10); Shell Oil (S. 31–33); Dr. Arthur Furst (API) (S. 7–10); B. F. Goodrich (S. 1); Mobay Chemical Co. (S. 20); Industrial Health Foundation, Inc. (S. 6); Ciba-Geigy (S. 6); American Telephone and Telegraph Co. (S. 4); Upjohn Co. (S. 6–7); Department of Energy (S. 3); Compton and Knowles (S. 3–4); AIA (S. 1); Phillips Petroleum (S. 5–6); Martin-Marietta Chemicals' (S. 3); Eli Lilly (S. 4); Miles Laboratories (S. 2–3); Burroughs Wellcome Co. (S. 2); Dyes Environmental and Toxicology Organization, Inc. (S. 9); Standard Oil Co. of California (S. 12–13); American Conference of Government and Industrial Hygienists (S. 7); Chemical Specialties Manufacturers Assoc. (S. 13); National Paint and Coatings Assoc. (S. 16); Bristol-Myers Co. (S. 32); Balchem Corp. (S. 2); Soap and Detergent Assoc. (S. 63); Union Carbide Corp. (S. 5–6); Dr. Harry Demopoulos (S. 16); Manufacturing Chemists' Assoc. (S. 31–32); Air Products and Chemicals (S. 6); GTE Service Corp. (S. 3–5); Stauffer Chemical Co. (S. 2); Organization Resources Counselors, Inc. (S. 54–56); Sherwin-Williams Co. (S. 16); ASARCO (S. 19).

as buffering for certain exogenous agents—the using up of certain conjugating agents, whether it is a sulfate or any of the others, which are detoxifying mechanisms, so that there are a variety of normal physiologic, homeostatic mechanisms within the cell which can effectively handle a dose below X and which cannot handle above X." (Tr. 8722)

Dr. Harry Skalsky (Reynolds Aluminum) commented:

"The MTD testing may also be criticized on other grounds. In any physiological system, a biochemical pathway may become overloaded and/or a secondary system be activated. Young and Gehring demonstrated a dramatic increase in the excretion of unchanged dioxane as a function of dose, suggesting that the hazard from a high dose of dioxane may be disproportionately greater than that from a lower dose.

"The possibility of changes in pharmacodynamics or metabolism of a compound has been ignored in maximum tolerated dose testing. With the amount of toxic stress on a test animal at the MTD dose, changes in the metabolism would be expected. That these parameters have not yet been measured discredits any data from maximum tolerated dose testing." (Tr. 7590)

Dr. John Zapp (Dupont) commented:

"Animals which metabolize a chemical differently from man cannot be expected to yield results comparable to man. Doses which overwhelm an animal's capacity to metabolize a chemical by its normal mode can lead to the accumulation of abnormal metabolites which produce effects which do not occur at doses which the animal can handle in its normal mode, and which therefore may lead to false conclusions regarding the effects of low doses in man." (Tr. 5266)

The National Agricultural Chemicals Association (NACA) commented:

"High doses may cause the formation of carcinogenic agents that are not formed at low dose levels, and thus negate the relevance of the animal tests." (NACA, S. 4)

Borden Chemical, Inc. commented:

"OSHA fails adequately to consider that when the dosage for an animal is massive, its natural detoxification systems or defense mechanisms . . . are usually overwhelmed . . . result is that the detoxification mechanisms of the host become incapable of providing the necessary protection." (Borden, 4)

Despite the number of comments proposing the importance of the mechanism of metabolic overloading, the actual scientific evidence presented in support of this hypothesis was very, very limited. Dr. Perry Gehring (Dow Chemical) cited his own work and that of his associate Dr. P. G. Watanabe on vinyl chloride in rats as an example of dose-dependent metabolic differences (Watanabe *et al.* 1976 a,b,c; References to Dr. Gehring's Statement). Dr. Gehring commented:

"It is absolutely essential in assessing risk that attention be given to dose because administration of large doses in accordance with the maximum tolerated dose concept frequently overwhelms the detoxification mechanisms of the body, resulting in disproportionate increase in the manifestations of toxicity, and this is inclusive of oncogenicity. In my testimony, I illustrate this simplistically with barrels having two slits. As the flow of fluid [dose] into the barrel increases, the capacity for escape of the fluid through the lower slit is overwhelmed. This leads to a buildup of the fluid in the barrel and escape by another slit.

"This, in reality, does occur in the body. Increasing the dose of many chemicals increases disproportionately the amount of the chemical retained in the body or the amount reacting with tissue, and in some cases, the amount entering alternate routes of biotransformation which produce reactive metabolites that react with tissue. In some cases, the depletion of critical constituents needed for detoxification by high doses may enhance greatly the reaction with tissue. For example, depletion of glutathione." (Tr. 5034–35)

As noted by NACA, Drs. Gehring and Watanabe drew the following conclusions:

"The primary detoxification pathway for VC involves conjugation of its reactive metabolites with nonprotein sulfhydryl groups. Therefore, it seems reasonable to postulate that as the nonprotein sulfhydryl groups are depleted, reactive metabolites will be free to react with other macromolecules (DNA, RNA, protein, lipids), resulting in toxicity and carcinogenicity.

"In summarizing the study on the pharmacokinetics and metabolism of VC, the data indicate that the fate of VC in rats is dose-dependent following either single oral administration or inhalation exposure. More importantly, it appears from the data available that a correlation exists between doses of VC that cause tumors and those that saturate metabolic or detoxifying pathways." (NACA, S. 22–23)

However, at least one of these conclusions appears to be in conflict with the results of Drs. Gehring and Watanabe. The authors showed (Watanabe *et al.* 1976b; Reference to Gehring Statement) that at high doses, diminished detoxification efficiency in fact correlates with a flattening of the dose-response curve for hepatic angiosarcoma, i.e., a *reduction* in the incremental increase in tumor incidence per unit increment in dose. In other words, the work of Drs. Gehring and Watanabe with vinyl chloride suggests an overloading of *toxification* mechanisms, not detoxification mechanisms. Subsequent to the hearing this point was stated more explicitly in another paper published by Dr. Gehring and his co-workers:

"For vinyl chloride-induced hepatic angiosarcoma in rats, a logarithmic probability plot (probit plot) of the incidence versus the amount of vinyl chloride metabolized, *v*, over a range of exposures from 50 to 10,000 ppm of VC gives a classical straight line (Fig. 2A). The dose-response relationship is not a straight line when plotted as a function of the exposure concentration, S (Fig. 2B). These results support further the conclusion that VC requires biotransformation to an active metabolite for tumorigenesis. Furthermore, a more reasonable evaluation of the dose-response data for vinyl chloride-induced tumorigenesis requires knowledge of the amount of VC activated as a function of exposure." (Gehring *et al.*, 1978, p. 586)

The authors then proceeded to distinguish clearly between this situation and the hypothetical case of overloading of detoxification mechanisms:

"For some chemicals detoxification of the chemical *per se* or reactive metabolites formed from the chemical may also be dose-dependent and saturable leading to a build-up of toxic materials. In such cases, the incremental responses to increasing doses or exposures will become disproportionately larger rather than smaller." (Gehring *et al.* 1978, p. 587, references omitted)

A recent letter in *Science* by Drs. K. Hooper, R. Harris, and B. Ames discussed Gehring's argument for dose dependent detoxification mechanisms and its relation to whether chemical carcinogens exhibit "thresholds":

"The first argument is that mechanisms detoxifying carcinogens are overwhelmed at the high dose levels often used in rodent bioassays, and a disproportionately large carcinogenic effect occurs at these doses. As an example, Gehring implies that at dose levels of vinyl chloride above 50 to 150 parts per million, where detoxification mechanisms may be saturated, a disproportionate increase in carcinogenic effect in rodents would occur. Yet the animal bioassay results of Maltoni (2), Lee *et al.* (3), and Viola *et al.* (4) on vinyl chloride suggest, if anything, just the opposite: as inhalation exposures increase beyond 150 ppm, the increase in carcinogenic response is *less* than that predicted from a linear extrapolation of the responses in the dose range 0 to 150 ppm (Fig. 1). Thus, the risk from exposure to low levels of vinyl chloride might be more than a millionfold higher than Gehring's estimate (5). Based on recent pharmacokinetic studies on vinyl chloride (6), the explanation for this proportionately greater activity at low doses may be that the mechanisms that *activate* vinyl chloride to the proximate carcinogen are saturated at high doses." (Hooper *et al.*, 1979, p. 602, figure omitted)

The authors concluded that Dr. Gehring's argument is inaccurate and does not support the contention that the risk to society from such chemicals would be negligible.

In any case, the argument appears to oversimplify the issue of the carcinogenesis of vinyl chloride, since

other evidence in the record showed that vinyl chloride induces several other tumor types in addition to angiosarcoma of the liver, and indeed is effective at very low doses (see Dr. Holmberg's Statement, and Maltoni, 1977).

The only other specific study cited by any witness in support of the concept of metabolic overloading was a study by Dr. Gehring on the carcinogenicity of dioxane (Kociba *et al.*, 1974; Reference to Gehring Statement). This study showed clear evidence of carcinogenicity only at the highest of three dose levels, which Gehring associated with a quantitiative shift in metabolic transformation:

"*Demonstration of Dose Dependency*—The excretion of ^{14}C-activity by rats given various doses of ^{14}C-dioxane also demonstrated dose-dependent kinetics; as the dose was increased, more dioxane *per se* was eliminated via exhalation; at low doses essentially all was excreted rapidly as beta-hydroxyethoxyacetic acid (HEAA) in the urine. Thus, the biotransformation of 1,4-dioxane to the *detoxification* product, HEAA, is a saturable process which is overwhelmed by increasing the magnitude of the dose. The marked retention of dioxane with an increasing dose led us to conclude that the metabolism of dioxane must be 'induced' markedly with repeated daily doses. 'Induced' means that an adaptation occurs whereby the capacity to metabolize dioxane is increased." (Gehring, S. 23–24, emphasis added)

Dr. Gehring went on to present data which:

". . . indicates that a dose of 1000 mg/kg/day caused a marked induction of the elimination of dioxane; 10 mg/kg/day did not cause induction. In plain language the metabolism of rats receiving 1000 mg/kg/day dioxane had markedly changed. Their responses to dioxane, whether toxicological or carcinogenic, are not extrapolatable to rats receiving low doses." (Gehring, S. 24)

However, these data do not clearly show a corresponding discontinuity in the dose-response relationship for tumor induction. Indeed the data presented in the paper by Kociba *et al.* (1974) for liver tumors (10/120 at the 1000 mg/kg/day dose level, 1/120 at 100 mg/kg/day, and 0/120 at 10 mg/kg/day) are exactly what would be expected if the dose-response relationship were linear and non-threshold. Other experiments have been reported in which 1,4-dioxane has induced excess tumor incidence in mice and rats at doses down to 240 mg/kg/day (NCI Carcinogenesis Technical Report 80, 1978; IARC, 1976, Vol. 11, pp. 244–256). Thus, although Dr. Gehring's data indicate dose-dependent changes in metabolism of 1,4-dioxane, there is no evidence that tumor induction occurred only above the dose-levels at which the metabolic shift took place.

As pointed out below, OSHA concludes, therefore, that the concept that "metabolic overload" can lead to tumor induction only at high doses is not adequately supported by the available data, even for vinyl chloride and 1,4-dioxane. Since these were the only chemicals for which evidence on "metabolic overload" was presented in the Record, OSHA could not conclude that testing at the EMTD is inappropriate, either in general or even for these specific chemicals. If better evidence is ever available for "metabolic overload", it may be appropriate to introduce this evidence in a rule-making on the specific substance as is pointed out below. Such evidence would be considered by OSHA under the criterion of Section 1990.144(d) when classifying a substance. However, the evidence presented in the Record on this topic would not warrant any change in the general definition of "potential occupational carcinogen" in that regard.*

Even if better evidence were available for the hypothesis of metabolic overload in specific cases, it is not clear how it would be used either in designing experiments or in interpreting results. No witness offered specific suggestions for the use of such data. For example, Dr. Paul Kotin (Johns-Manville) was asked whether the biochemical and physiological effects which he had discussed were sufficiently measurable so that one could measure no-effect levels and use them to modify the definition of maximum tolerated dose: he replied that he had "never done that" (Tr. 8723). Dr. Harry Skalsky (Reynolds Aluminum) recommended that specific efforts should be made to establish that a compound is metabolized in the same manner at both lower and higher doses (Tr. 7590). However, he did not offer any prescription as to what should be done if such information is not available or if differences are found.

A recent publication of the Food Safety Council (*Proposed System for Food Safety Assessment*, 1978) recommended that the high dose in chronic testing should be defined as one which "takes into consideration metabolic and pharmacokinetic data . . .". However, the way in which such data would be taken into consideration was not stated, and the report explicitly recommended that:

". . . if dose-dependent qualitative or quantitative differences occur, at least one test dose should be set above the metabolic shift . . ." (Food Safety Council, 1978, p. 102)

Although this recommendation is not operationally explicit, the Council appears to be recommending that high test doses be used even if there is evidence for dose-dependent metabolism of the kind discussed by Gehring and others.

This issue was put into perspective by Dr. Umberto Saffiotti (NCI) in his prepared testimony:

"An objection has been expressed over the validity of results of tests conducted at very high exposure levels. This objection is based on a hypothetical condition: that the metabolic pathways for carcinogenic activation of the test chemical may be *qualitatively* different in a critical manner at high and low levels of exposure, so that the chemical becomes completely and totally detoxified up to a certain level of exposure, while at high dose levels the detoxification mechanism is "overloaded" and carcinogenic metabolites begin to be produced and become effective. If this hypothesis were proven to be correct, and if in addition we could demonstrate that no extraneous influence would alter these control mechanisms, and if we could then demonstrate the level at which "overflow" occurs, and then establish a valid method for predicting this "threshold level" reliably, and finally if we could be sure that this hypothetical methodology applies to the case being considered, and to all conditions of human exposure and to all exposed individuals with their varying susceptibilities, then—at last—we would indeed be able to assure that the carcinogenic effect observed in tests at high levels of exposure is not relevant for the prediction of hazards in people at much lower levels.

"At this time such a hypothesis remains unsubstantiated and its applicablity to the determination of human safety based on animal test data is unwarranted. Metabolic pathways of carcinogen activation do indeed change quantitatively from species to species even with major dose level changes, but the evidence is that the changes are in the relative proportions of different metabolites rather than in their abrupt disappearance at fixed levels. Many chemical agents, both endogenous and exogenous, can alter the enzymatic systems which control carcinogen activation, for example concurrent exposures to other carcinogens. Individual thresholds of susceptibility to given carcinogens indeed exist, i.e., it is a matter of simple observation

* A number of other witnesses also argued during oral testimony that testing at high doses was inappropriate due to metabolic overload of detoxification mechanisms: Dr. Robert Olson (St. Louis Univ.), Tr. 3238; Dr. James Jandl (Harvard Univ), Tr. 3348; Dr. Leonard Goldwater Tr. 3538–9; Mr. Carroll Kirwin (Phillips Petroleum), Tr. 4206–7; Dr. A. E. M. McLean (AIHC), Tr. 4845–6; Dr. William Lederer (Manufacturing Chemists Assn.) Tr. 4795–6; Dr. Leon Goldberg (Chemical Industry Institute for Toxicology), Tr. 6488–9; Dr. Ralph Freudenthal (Stauffer Chemical Co.), Tr. 6751–3; Dr. Arthur Furst (API), Tr. 6932; Mr. John Yost (Muskegon Chemical Co.), Tr. 7311; Dr. Marshall Hahn (Georgia Pacific Co), Tr. 7933–4; Dr. Paul Gross (Industrial Health Foundation), Tr. 8320. However, none of these witnesses cited any specific evidence additional to that of Dr. Gehring cited above. Thus, although the belief in the concept of "metabolic overloading" is evidently widely held, the only evidence adduced to support it appears to be the work of Gehring on dioxane, which OSHA judges to be inconclusive.

that not everybody who is exposed to a carcinogenic agent develops a cancer from it in a lifetime. Those who do are the most susceptible individuals. The entire basis of preventive medicine is directed towards the protection of susceptible individuals.

"If all the necessary elements of evidence were assembled to provide unquestionable proof that a carcinogenic effect obtained at high doses is due to a mechanism of action which is specifically different from that at low doses and completely inoperative at low doses, in all exposed individuals, then this evidence—if critically valid—would constitute good ground for rejecting the assumption of a carcinogenic risk at low levels. I have not seen any such documentation so far for any chemical carcinogen. I believe that it is not likely to be developed in the near future, because of current methodological limitations. If it were developed, it may most likely concern a single or a few individual chemicals rather than the generality of exposures. Should these exceptional cases emerge with the progress of research—as I very much hope they will—the proposed OSHA policy can implement the necessary exceptions through its flexible provisions for judgmental evaluations implicit in the term "causes" discussed above, and through its provisions for rebuttal." (Saffiotti, S. 12–13)

Referring to this statement Dr. Saffiotti during his oral testimony concluded:

"What this statement to me implies is that we are really dealing with a very theoretical possibility, and it is not anything so practical that we can use it as a basis for regulation in the everyday world. (Tr. 877)

Dr. Robert Squire (Johns Hopkins) agreed with Dr. Saffiotti on this point:

". . . if thorough metabolic, biochemical, and genetic studies clearly demonstrate that no electrophilic or genetically toxic moieties are produced by a particular chemical, that chemical may give rise to less concern than one capable of an irreversible interaction with macromolecular targets. Carcinogenic potential, if present, would more likely depend on a promotional or secondary mechanism. In this case, I would not feel it necessary to test at a toxic level. However, very few compounds have yet been studied enough to justify such treatment. "(Squire, S. 23)

On the question of metabolic overload which may alter the effects of a compound under testing, Dr. Curtis Harris (NCI) commented:

"I do not think there is any evidence for that. I think perhaps one of the things that we are—that Mr. Schwartz was trying to bring up—maybe that is what he meant by metabolic overload. That is a very hypothetical situation in which—I do not know of any really good data to show that that is the case. And there are so many assumptions based in that hypothesis, that it is to me exceedingly unlikely." (Harris,Tr. 2009)

In discussing metabolic differences between species, Dr. William Lijinsky (NCI–FCRC) commented:

"We do not know enough about the mechanism of action of any carcinogen, even the much studied ones, to be able to make judgments of the significance of similarities or differences in metabolism of a substance in man versus animals in evaluating a carcinogenesis test. There is no reason to believe that metabolic overloading of the animal will lead to tumor induction in animals by a non-carcinogen; metabolic overloading is likely to lead to a diminution of carcinogenic effectiveness of a substance because of excretion of much of the dose unchanged. (Lijinsky, S. 30)

During his oral testimony Dr. Lijinsky explained:

"So we want to use as high a dose as we can. However, we do not want to use a dose so high that it upsets the dynamics of the body in such a way that the animals die early, for example. The main reason that we do not—that we use a maximally tolerated dose and not the maximum dose is that we do not want the animals to die before the end of their normal lifespan, so that we are sure we give the greatest possible opportunity for tumors to develop. That is the reason we adopted a maximally tolerated dose, not a maximal dose. It has nothing to do with differences of metabolism." (Lijinsky, Tr. 1076)

For the vast majority of substances, such evidence is lacking. If it could be demonstrated that at high dose levels qualitative and quantitative differences occur in metabolism which preclude the possibility of carcinogenic risk in the test animals, and if it can be shown that humans will respond the same as the test animals, then a high test dose would not be relevant to human risk. Short of this, high test doses are required to assure that potential carcinogenic risks to sensitive segments of the human population are avoided.

3. *Definitions of EMTD.*

(a) As has been discussed earlier, the Record in this proceeding has demonstrated considerable misunderstanding and confusion about the concept of EMTD and how EMTD levels should be selected. Controversy surrounding the use of EMTD appears therefore to be in part a result of misunderstandings over the meaning of the term itself or how it is operationally utilized in practice, rather than a substantive difference in opinion regarding the appropriateness of using high dose levels in screening tests. There is, in fact, no precise definition of EMTD and logical debate and discussion leading to consensus is therefore difficult. Descriptions of the EMTD by experts in carcinogenesis have varied from "doses which induce significant levels of mortality to assure that a potential carcinogenic risk is not missed" to "levels which do not involve any degree of toxicity".*

An important point which was widely overlooked by some witnesses at the hearing is that it is impossible to establish criteria for defining EMTD in terms of survival and toxic effects observed during a lifetime experiment, unless the experiment is to be carried out twice. In fact, an operational definition of EMTD must be based on observations during a preliminary (subchronic) experiment. This is evidenced in the most recent definition formulated for the National Cancer Institute Bioassay Program *(Guidelines for Carcinogen Bioassay in Small Rodents,* National Cancer Institute, 1976; Appendix 1 to Griesemer statement):

"*A maximum tolerated dose* (MTD) should be selected for each sex of each strain to be used in the chronic study. The MTD is defined as the highest dose of the test agent given during the chronic study that can be predicted not to alter the animals' normal longevity from effects other than carcinogenicity. The MTD is estimated after a review of the subchronic data. Since these data may not always be easily interpretable, a degree of judgment is often necessary in estimating the MTD. The MTD should be the highest dose that causes no more than a 10% weight decrement, as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span." (Sontag *et al.,* 1976, pp. 14–15, footnote omitted)

Other examples of definitions of EMTD presented in the record are as follows:

PPG Industries:

"An adequate definition incorporating all of the essential parameters to enable an appropriate and realistic MTD to be selected [does] not yet exist. Treatment levels which cause detectable or measurable hematological, enzymatic, pathological and behavioral changes, in addition to weight gain, depression, and early mortality, must enter into the selection of a proper MTD. When a realistic and appropriate MTD is defined incorporating the above points, there will be fewer arguments as to the appropriateness of the study results." (PPG Industries, S. 22)

Dr. Harry Skalsky (Reynolds Aluminum):

"The use of high dose testing by F.D.A., E.P.A., and O.S.H.A. is based on the premise that there is no minimum dosage of a carcinogen. Testing of this type uses the

*What is clear, however, is that it just is not true that "(t)esting of this type uses this maximum tolerated dose or the dose at which the animal is just able to survive." (Skalsky, Reynolds Aluminum, Tr. 7589). In fact, as pointed out above, such a situation gives rise to false negative results, not false positive.

maximum tolerated dose (MTD) or the dose at which the animal is just able to survive. (Skalsky, S. 8)

Dr. Benjamin Van Duuren (New York Univ.):

"It is to do a two or three month short-term evaluation of the toxicity of a compound, and what we define as the maximum tolerated dose is the dose that does not give rise to weight loss or early death, or other acute toxic effects in animals . . ." (Tr. 1881–1882)

FDA (1971):

"Testing should be done at doses and under experimental conditions likely to yield maximum tumor incidence. This would mean the use of doses several orders of magnitude above the actual use level." (FDA Panel, 1971 p. 433)

Health Protection Branch of Canada (1973):

"In carcinogenesis testing, the highest dose level should be within the toxic range, but should be consistent with the prolonged survival of the majority of animals. The lower levels should permit the animals to survive in good health for their natural life span or until tumors develop." (Health and Welfare, Canada, 1973, p. 19, reference omitted)

Subsequent to the hearing, the Food Safety Council (*Proposed System for Food Safety Assessment*, 1978.) presented a review of factors involved in selecting dose levels, and made the following recommendation:

". . . the high dose in chronic testing should be defined as one which [in] a subchronic study:

"1. Induces no overt toxicity, i.e., appreciable death of cells or organ dysfunction as determined by appropriate clinical, pathological, or biochemical methods.

"2. Induces no toxic manifestations which are predicted to shorten the lifespan of the animals except as the result of neoplastic development.

"3. In two generation studies, is not detrimental to conception rates, fetal or neonatal survival, or postnatal development.

"4. Does not retard weight gain during the subchronic test by greater than 10% as compared to control animals.

"5. Takes into consideration metabolic and pharmacokinetic data, and if dose-dependent qualitative or quantitative differences occur, at least one test dose should be set above the metabolic shift (provided the level(s) does not exceed the criteria listed above in 1 through 4)." (Food Safety Council, 1978, p. 102)

This recommendation and the NCI *Guidelines for Carcinogen Bioassay in Small Rodents* have three key features in common: (i) the EMTD is to be selected on the basis of results observed in a subchronic study; (ii) it is appropriate to select a dose level which induces minor toxic effects and up to 10% weight loss even in the subchronic study; (iii) the selection of the EMTD involves the *prediction* of survival during the chronic test. Neither these definitions nor others in the Record require that there should be no manifestations of toxic effects after exposure at the EMTD for a lifetime. Nor does OSHA believe that there is any documented evidence in the Record that would invalidate positive results observed in a lifetime study in which toxic effects or reduced survival occurred.

(b) Several witnesses cited examples of studies in which toxic effects or reduced survival were reported in long-term bioassays. Some witnesses suggested that those effects indicated that the EMTD had been exceeded (Dr. Robert Olson (St. Louis Univ.), Tr. 5024; PPG Industries, S. 24). However, although these witnesses implied that the results of the experiments were unreliable, none actually stated that the results should be discarded altogether. Perhaps the clearest statement is that of Dr. Leon Golberg (CIIT), as follows:

"In the present instance, an appraisal of the 'state of the art' is made possible by an analysis of the carcinogenesis bioassay data considered over the past two years by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens of the National Cancer Institute. In Table II, a summary is provided of some of the salient features that emerge, illustrating a number of difficult issues, some of which were found by the Subgroup to need consideration. What this table tells us is that the protocols and conduct of bioassays carried out in the recent past leave much to be desired. I know that changes have been made in an effort to correct some of these deficiencies. Nevertheless, the heritage of just this one program has provided a record of hundreds of tests whose *results cannot be taken at their face value for automatic decisions* on carcinogenic potential. For purposes of assessment of risk to man, *the full data forthcoming from each test will need careful evaluation* by appropriate experts who will consider them in the context of all the available information on the compound in question, not solely on the basis of the test results forthcoming from the carcinogenesis bioassays." (Golberg, S. 2–3, emphases added)

The evidence on this issue was summarized by AIHC in its Post Hearing Brief, as follows:

"Similarly, Dr. McLean testified that large doses can alter metabolic pathways and injure tissues, making it difficult to extrapolate from MTD doses (Tr. 4845–4846). Dr. Olson also emphasized that MTD can incapacitate or injure organ systems leading, for example, to renal damage as well as neoplastic lesions (Tr. 3238). Dr. Olson referred specifically to the MTD bioassay on trichloroethylene where there was evidence of renal and cardiac damage (Tr. 3244). Exhibit 83 is a statement by Dr. Bernard Oser, presented to the National Academy of Science committee evaluating saccharin, in which he refers to the organ damage which raised questions about the results of the experiments on saccharin. Similarly, Dr. Furst discussed the consequences of physical damage from an excessive dose. (Furst S. 7–9, Tr. 6931–6932, 6947–6948.)

* * * * *

Thus, Dr. Golberg testified, if the MTD is not selected properly, massive nonspecific tissue damage can result. *Id.* at 4. This can lead to carcinogenic results by a "Secondary mechanism"—tissue damage. (Golberg S. 4–6, Tr. 6484–6491.) The questionable relevance of a positive result from secondary carcinogenesis was recognized, Dr. Golberg said, by the Food and Drug Administration in the case of selenium and by investigators in the case of antithyroid action of substances in rats which have no counterpart in man." (Golberg S. 5–6.) (AIHC Post Hearing Brief, pp. 134–135; Hearing Exhibit 251)

The notation of "secondary carcinogenesis" was presented in great detail by Dr. Leon Golberg (CIIT):

"One of the consequences of nonspecific tissue damage (Pozharisski, 1975) that may be produced by compounds administered at the MTD is carcinogenesis by a "secondary" mechanism. Here is a well-recognized concept that was utilized by the Food and Drug Administration to account for the production of liver cancer by high doses of selenium, which is an essential nutrient at low doses (**Federal Register**, 1973, 1974). The important principle of secondary carcinogenesis is much more widely applicable (Kolbye, 1976), although its implications have not been adequately explored. Suffice it to say that the production of cancer by secondary mechanisms is an instance where the end-result is not necessarily indicative of carcinogenic potential of the compound responsible for the effect. In some cases of this sort, a threshold is demonstrable for the production of the primary effect that elicits this secondary neoplastic change. Thus, in considering selenium, the Commissioner of the Food and Drug Administration pointed out that consumption of beverage alcohol "is associated with a higher incidence of liver cirrhosis, which, in turn, is associated with a higher incidence of liver cancer. Other common agents, at high levels, may produce the same result." He drew the conclusion that such substances "are not, by reason of their capacity to induce liver damage when abused by being consumed at high levels, properly classified as carcinogenic because of their potential association with a higher rate of liver cancer."

"One may extend the illustrations of secondary mechanisms of carcinogenesis to the area of antithyroid action that results in thyroid epithelial hyperplasia which, if continued long enough, eventually leads to neoplasia. This is the mechanism by which iodine deficiency elicits thyroid cancer in rats (Doniach, 1970b; Lupulescu and Petrovici, 1968) but, apparently, does not lead to thyroid cancer in people (Doniach, 1970a). Thyroid hyperplasia is produced in rats by dietary goitrogens, certain sulfonamides and antithyroid agents (Astwood, Sullivan, Bissell and Tyslowitz, 1943). What is more, the high

rate of apparently spontaneous follicular hyperplasia in the thyroids of old rats makes this species an unsuitable model for man. A further example of "secondary" carcinogenesis is the production of bladder stones by compounds like diethylene glycol (Weil, Carpenter and Smyth, 1965, 1967). In rats and mice the presence in the urinary bladder of such stones or other foreign bodies is associated with the development of urothelial hyperplasia, papillomas, and ultimately carcinomas (Toyoshima and Leighton, 1975). These illustrations emphasize the need for careful analysis and expert judgment in interpreting observations on carcinogenesis, in view of the importance of distinguishing primary from secondary pathological events. Only in this way can one assess the role played by the particular MTD of the compound used in any given bioassay, in eliciting the primary changes." (Golberg, S. 4–6)

The hypothesis of "secondary carcinogenesis" was also discussed by Dr. Francis J. C. Roe (AIHC), who proposed as examples of secondary carcinogenic mechanisms the production of bladder stones (ethylene glycol, polyoxyethylene(8)monostearate) and tissue damage in the testis (cadmium) (Roe, S. 24, 68). Dr. Robert Olson (St. Louis Univ.) cited the NCI bioassays for trichloroethylene and tetrachloroethylene as examples of tests in which the high doses used caused:

". . . tissue damage unrelated to tumor formation . . . . These procedures violate the rules of good practice in toxicology, and make extrapolation of results from animals to man impossible." (Olson, S. 11, Tr. 5034)

PPG Industries similarly cited the NCI Bioassay for 1,2-dibromoethane:

"The NCI study (gavage) on 1,2-dibromoethane used doses which resulted in a high incidence of squamous cell carcinomas of the forestomach and death. Treatment levels in excess of the MTD by NCI definition were used. With all of the uncertainties in bioassay programs conducted for NCI, the agencies consider them as conclusive. This stance is untenable. (S. 23)

OSHA concludes that the hypothesis of secondary carcinogenesis is not supported by a substantial body of empirical evidence. The examples of induction of bladder stones provide at best circumstantial evidence of association between the effects, not evidence for a causal connection (see Saffiotti, Tr. 937–938). In the case of saccharin, where induction of bladder stones has been proposed repeatedly as an explanation for the positive results, analysis of the actual data indicates that this hypothesis is incorrect. Indeed, the test data on saccharin have been reviewed repeatedly by expert committees, which concluded that saccharin is correctly categorized as a carcinogen in rats (OTA, 1977, NAS, 1978).

Among the other examples cited, the evidence for carcinogenicity of selenium is at best inconclusive (IARC, 1975; NAS, 1976; Squire and Goodman, Post-hearing Comment, p. 6; Saffiotti, Post-hearing Comment, p. 2; Furst, Tr. 6947). Beverage alcohol is well recognized as a cause of cancer in humans, acting not only in the liver, but also in the mouth and esophagus (Rothman and Keller, 1972; USDHEW, 1978; Peto, 1977; Rothman, 1975 pp. 139–150). Dr. Roe himself questioned whether the testicular lesions caused by cadmium were in fact neoplasms (S. 24), and in any case cadmium compounds are recognized as carcinogenic in humans resulting from occupational exposure (Tomatis *et al.*, 1978). And in the cases of trichloroethylene and tetrachloroethylene, there was an increased tumor incidence in mice exposed to both dose levels, even though the male mice exposed to the low doses of tetrachloroethylene and the female mice exposed to the low doses of trichloroethylene showed little or no reduction in survival relative to controls (NCI Carcinogenesis Technical Reports, 2, 13, 1976–77).

Finally, if the dose levels in a bioassay are chosen at too high a level, so that the animals die prematurely, this would *reduce* the probability of observing a positive result rather than being likely to give rise to a false positive. This is reflected in the definition of EMTD proposed by the FDA Advisory Committee on Protocols for Safety Evaluation: ". . . [one] likely to yield maximum tumor incidence" (FDA 1971). (See also Griesemer, Tr. 935–936)

Those who would urge OSHA to reject data from tests conducted at "too toxic" doses would presumably wish OSHA to ignore data such as those on 1,2-dibromoethane, which induced multiple-site tumors at both dose levels in both sexes of rats and mice within 60 weeks of exposure, at incidence rates up to 94 percent (NCI Carcinogenesis Technical Report 86, 1978).* OSHA believes that it would be improper to ignore such overwhelming evidence of hazard.

c. OSHA's Conclusions

OSHA intends, therefore, to use data obtained from bioassays conducted at "any level of exposure or dose" to support the finding of carcinogenicity of a substance. If truly substantial scientific data are available to support a hypothesis of "metabolic overloading", "secondary carcinogenesis" or some other non-specific mechanism of action, OSHA is willing to consider such data, provided that they meet the criteria set out below. However, there was no substantial evidence in the Record (other than speculation or hypothesis) to justify any modification in the general definition of "potential occupational carcinogen."

Specifically, OSHA concludes that small numbers of test animals may serve as appropriate "surrogates" for large populations of humans; a specific cancer response in 1% of the work population would be a major health disaster, but such a response would go undetected in 50–100 test animals. Since carcinogenic response is usually dose related, the biological and statistical sensitivity of a bioassay may be enhanced by increasing the exposure levels of the test substance rather than the less feasible alternative of increasing the number of test animals to match the human population at risk.

The EMTD is determined on the basis of pre-chronic tests and other relevant information. If the actual conduct of a test reveals that the EMTD is too high to meet the conditions defined above, clear positive results obtained above the EMTD are acceptable as evidence of carcinogenicity unless there is convincing evidence to the contrary as discussed below. On the other hand, non-positive results obtained above the EMTD are generally considered inadequate, unless particularly strong and specific scientific reasons justify their acceptance as non-positive. Positive results obtained at or below the EMTD provide evidence of carcinogenicity.

Although, as specified above, none of the evidence presented in the Record relative to the concepts of "metabolic overloading" or "secondary carcinogenesis" was scientifically sound and/or convincing, OSHA will consider such evidence for a specific substance subject to rulemaking if better evidence is provided in the future. In this regard, OSHA believes that it is appropriate to require that certain criteria, which such evidence on specific substances must satisfy before any evidence will be considered in the substance-by-substance rulemakings, be met. These criteria have been developed after a detailed review of the substantial evidence in the Record, specifically that discussed in Section V.D. 3(b) above. The minimum criteria are as follows. Section 1990.143(g) provides that:

*Again, EPA has accepted the results of the NCI bioassay for 1,2-dibromoethane as positive for carcinogenicity, and has initiated regulatory action (42 FR 63139–63140).

(g) *Use of high doses in animal testing.* Positive results for carcinogenicity obtained in mammals exposed to high doses of a substance will be used to establish the qualitative inference of carcinogenic hazard to workers. Arguments that such studies should not be relied upon will be considered only if evidence which meets the criteria set forth in Section 1990.144(d) is provided.

And section 1990.144(d) provides:

(d) *Use of high doses in animal testing.* Arguments that positive results obtained in carcinogenesis bioassays with experimental animals subjected to high doses of a substance are not relevant to potential carcinogenic risks to exposed workers will be considered by the Secretary only if the evidence for the specific substance subject to the rule-making meets the following criteria:

Criteria. (i) Documented evidence is presented to show that the substance in question is metabolized by the experimental animal species exposed at the dose levels used in the bioassay(s) to metabolic products which include one or more that are not produced in the same species at lower doses.

(ii) Documented evidence is presented to show that the metabolite(s) produced only at high doses in the experimental animal species are the ultimate carcinogen(s) and that the metabolites produced at low doses have been tested and not been found to be carcinogenic; and

(iii) Documented evidence is presented to show that the metabolite(s) produced only at high doses in the experimental animal species are not produced in humans exposed to low doses.

In the hypothetical case of "metabolic overloading", at least three specific points need to be addressed before such evidence can have any scientific bearing on the points at issue. First, it needs to be shown specifically that "metabolic overloading" actually takes place—i.e., at high doses one or more metabolic products are produced which are not found at all at doses low enough to be relevant to occupational exposure. (It is obviously scientifically insufficient simply to show a difference in relative yields of different metabolites, or of metabolite and unchanged material, since at best such evidence would be relevant only to quantitative estimation of risk.)

Second, it needs to be shown that one or more of the products produced only at high doses are the exclusive cause of the carcinogenic effect and that the metabolites produced at low doses have been tested and not been found to be carcinogenic. (Dr. Gehring's data on vinyl chloride fail in this respect).

Third, it needs to be shown that the same type of "metabolic overloading" would result in humans—i.e., that the metabolites produced in the animals only at high doses would not be produced in humans under occupational exposure conditions. To make a convincing showing in this regard, substantial evidence on metabolism in humans would be required (see Section V.D. 13 below).

In the case of other mechanisms of "secondary carcinogenesis", it is more difficult to specify precise operational criteria for the consideration of evidence. In general, OSHA will require that definite evidence be presented for the substance subject to rulemaking that a "secondary" mechanism of carcinogenesis can reasonably be involved to explain the observations. Specifically, OSHA will require that a reasonable scientific showing be made that the mechanism of action of the specific substance has been demonstrated, and, *in addition,* that this mechanism would not operate at exposure levels relevant to occupational conditions. (For example, if it is hypothesized that a carcinogen operates at high doses by inducing the formation of bladder stones, it should be shown (i) that the excess cancers are associated individually with bladder stones; (ii) that bladder stones are induced only at high doses; and (iii) that neither bladder stones or tumors are induced at lower doses.)

OSHA has provided for the consideration of such data in § 1990.144(f), which provides criteria for the consideration of claims that carcinogenic effects result from these or other *Indirect Mechanisms* (see Section V.D.I above).

OSHA's purpose in specifying these criteria is to encourage the submission of scientific data that genuinely support the scientific inferences of "metabolic overloading" or "secondary carcinogenesis" in specific cases, while avoiding wasting time and resources on the repetition of scientifically insufficient discussions of these issues in the future.

4. Organ Specificity

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA took the position that positive results in any mammalian species and "at any organ or site" would be considered relevant in the identification and regulation of any toxic substances as a potential occupational carcinogen. In the preamble (42 FR 54162), OSHA cited two reviews in support of this position, *viz*:

"In experimental carcinogenesis, the type of cancer seen is often the same as that recorded in human epidemiological studies (e.g., bladder cancer in man, monkeys, dogs, and hamsters with beta-naphthylamine). In other instances, however, a chemical will induce neoplasms at different sites in different animal species (e.g., benzidine, which induces hepatic carcinoma in the rat, but bladder carcinoma in man; or chloroform, which induces hepatic carcinoma in the mouse, but kidney carcinoma in the rat) (IARC Monographs, Vol. 1, p. 10; 41 FR 15026; NRC Pest Control, Vol. 1, pp. 74–82). Thus there can be no presumption that the organ affected in animal experiments would necessarily be that at risk in man." (42 FR 54162)

b. The Public's Response and OSHA's Evaluation

There was general and virtually unanimous support for the proposed position that carcinogens are not normally organ-specific or species-specific. Indeed, only one substantial issue was raised during the rulemaking. A number of witnesses argued that some strains of mice have unique characteristics which make them particularly susceptible to the induction or enhancement of tumors at certain sites, primarily the liver, lung, mammary gland and lymphoreticular system. The evidence for this position was reviewed in detail under section V.D. 1 above (*Mammalian Species*) and was found to be insufficient to justify any exception to the basic proposition. Except for that issue, no other documented evidence was presented that would indicate that a positive result in one organ of one species would not be indicative of a potential risk to exposed humans regardless of the organ or site at risk in humans.

A review of the findings of the IARC Monograph program was presented by Dr. Lorenzo Tomatis (IARC) and others (Tomatis, *et al,* 1978; Appendix 5 to Tomatis Statement; Appendix G to Rall Statement). After reviewing the results of experimental studies in animals with 26 chemicals or industrial processes reported to be carcinogenic in humans, Dr. Tomatis (IARC) made the following generalization:

"Comparison between target organs in humans and animals confirms that the carcinogens have, in some cases, the same organ specificity in humans and experimental animals. In most cases, the chemicals were tested in more than one animal species, but the similarity in organ specificity may be limited to only one of the animal species tested. The chances for similar target organs are apparently greater if similar routes of exposure are used (Table 2). However, chemicals which were found carcinogenic in both humans and animals were carcinogenic in the latter also when administered by routes different from the one by which humans are exposed. The target organs in animals are more often multiple than in man." (Tomatis, *et al.,* 1978, p. 881; Appendix 5 to Tomatis Statement)

Examples of chemicals which affected different organs in humans and animals were given in Table 2 of Tomatis, *et al.,* 1978, omitting data on tumors at the site of administration.

Chemical	Target organ and (route) in humans	Animal species	Target organ and (route)
Aflatoxins	Liver (oral, inhalation)	Rat	Liver, stomach, colon, kidney (oral); liver, trachea (intratracheal).
		Mouse	Lung (i.p. injection).
4-aminobiphenyl	Bladder (skin, inhalation, oral)	Mouse (newborn)	Liver (s.c. injection).
		Rat	Mammary gland, intestine (s.c. injection).
Auramine (manufacture of)	Bladder (skin, inhalation, oral)	Mouse, rat	Liver (oral).
		Rat	Local, liver, intestine (s.c. injection).
Benzidine	Bladder (skin, inhalation, oral)	Mouse	Liver (s.c. injection).
		Rat	Liver (oral); Zymbal gland, liver, colon (s.c. injection).
		Hamster	Liver (oral).
Cadmium using industries	Prostate, lung (inhalation, oral)	Rat	Local, testis (s.c. or i.m. injection).
Cyclophosphamide	Bladder (oral, injection)	Mouse	Haemopoietic system, lung (i.p., s.c. injection); various sites (oral); bladder (i.p. injection).
		Rat	Mammary gland (i.p. injection); various sites (i.v. injection).
Diethylstilbestrol	Uterus, vagina (oral)	Mouse	Mammary gland (oral); mammary, lymphoreticular, testis (s.c. injection, s.c. implantation).
		Rat	Mammary, hypophysis, bladder (s.c. implantation).
		Hamster	Kidney (s.c. injection, s.c. implantation).
		Squirrel monkey	Uterine serosa (s.c. implantation).
Melphalan	Haemopoietic system (oral, injection)	Mouse	Initiator (skin); lung, lymphosarcoma (i.p. injection).
Mustard gas	Lung, larynx (inhalation)	Mouse	Lung (inhalation, i.v. injection), local, mammary (s.c. injection)
2-naphthylamine	Bladder (skin, inhalation, oral)	Mouse	Liver, lung (s.c. injection).
N'N-bis(2-chloro-ethyl)-2-naphthylamine	Bladder (oral)	Mouse	Lung (i.p. injection).
Vinyl chloride	Liver, brain, lung (skin, inhalation)	Mouse, rat	Lung, liver, blood vessels, mammary, Zymbal gland, kidney (inhalation).

This table shows that for more than half of the known human carcinogens which have been adequately tested in animals, tumors were induced in one or more animal species at organ sites different from those at which tumors are induced in exposed humans. In particular, it should be noted that for nine chemicals, tumors were induced in the liver and/or lungs of experimental mice, but at different sites in humans. Thus, at least for these substances, the induction of liver and lung tumors in mice indicates the existence of a qualitative hazard to humans, but does not indicate the organ site at risk.

Dr. Curtis Harris (NCI) dealt with the concept of organ or species specificity. He stated:

"The term 'organ-specific' I think is very bad. I think it should be changed to 'organ predominance' because I do not know of a chemical that causes cancer only in a single organ in an experimental animal species and in no other, where it has been adequately tested." (Harris, Tr. 2005)

"I do not think there are sex-specific carcinogens just as there are not species-specific carcinogens". (Harris Tr. 2006)

When asked specifically about target organs in animals for which there is no human analog, such as the Zymbal gland or forestomach, Dr. Harris (NCI) replied:

"Well, I do not think that makes me feel any more comfortable. That is one aspect of it. The other aspect is that usually the carcinogen causes tumors in multiple organs, and it may appear with a greater frequency in the Zymbal gland than in the breast, but it is almost—first of all, it would not make me feel any more comfortable, and second, that I frankly do not know of any carcinogen that causes only tumors of the Zymbal gland. Maybe there is such, but I am just not knowledgeable about that." (Harris, Tr. 2005)

Dr. Benjamin Trump (Univ. of Md.) also stated that:

". . . it is impossible to predict from one animal to another where the neoplasm is going to occur, and there are many examples where it occurs in one species in one organ, and another in another, and there are many factors involved in that." (Trump, Tr. 2005–2006)

To illustrate this point he described the following study:

"In that lead study that I mentioned, there is an excellent example of that with the compound alone, fluorobiphenyl acetamide, predominantly both liver and kidney, but many more liver. Adding lead greatly diminished the number of liver tumors; greatly increased the number of kidney. In humans exposed to varieties of—bombarded by all kinds of things, there is no way to predict." (Trump, Tr. 2006)

Dr. Umberto Saffiotti (NCI) commented in his direct testimony:

"Caution must be exerted when considering possible implications for humans of the organ[o]tropic effects of carcinogens observed in experimental models. Many carcinogens show markedly different organ specificity in different host conditions: therefore specific organotropic effects of the exposure to a given carcinogen in humans are often unpredictable from animal bioassays."

* * * * *

"Positive results of carcinogenesis studies in two mammalian test species constitute a solid basis of evidence for the presumption that a substance is a carcinogen and that exposure to it should be minimized. The two species may not respond in the same way to the carcinogen: neoplasms may develop in different tissues and organs and they may show different degrees of differentiation and malignancy. In this respect one should not expect to replicate exactly the same type of neoplastic response to different species. Similarly one should not expect the same type of carcinogenic response in humans and in a given test animal.

"The two-species requirement in the proposed policy has primarily a confirmatory value. *No evidence exists that carcinogens are species-specific.* Those that were found positive in one species and that were studied widely enough in other species were usually found to be positive in more than one species." (Saffiotti, S. 22, 29–30)

Dr. Bernard Weinstein (Columbia Univ.) also discussed this issue:

"There are known carcinogens which produce their carcinogenic effects at specific sites in different animal systems. However, the concept of site specificity is not completely understood at the present time. Certain factors have been identified, including: exposure levels, i.e., if certain tissues are directly exposed to the agent, then they become the responsive site; ability to metabolize the compound, which varies among tissues; rate of delivery to tissues; exposure via excretory pathways; differences in rates of proliferation of tissues; and differences between tissues in the repair of damage to cellular DNA. This is a complex process with numerous influencing factors, and *I do not believe that any conclusions about the safety of compounds can be drawn* on the basis of the site specificity." (Weinstein, S. 5)

Dr. William Lijinsky (NCI–FCRC) commented at length on problems of defining organ and species specificity:

"Equally baffling in our attempts to study human cancer through experiments in animal models is the matter of species specificity and organ specificity. This is what bedevils risk extrapolation based on the results of simple chemical or biological tests also. We have no idea where man is placed in the scale of susceptibility to chemical carcinogens except in the few unfortunate cases in which we have been able to count the number of people who developed cancer after known exposure to industrial chemicals. Aflatoxin is the most potent carcinogen known—for rats—in which it induces liver cancer at very small doses. However, it appears to be completely noncarcinogenic in mice and active in monkeys only at quite high doses. This is a carcinogen to which man is exposed, and we suspect that these exposures contribute to human cancer risk in some areas of the world. However, we have no idea what that contribution is or how it relates quantitatively to carcinogenic risks from other parts of the environment, such as diet and medicines (several antimalarials and drugs used to treat infectious diseases in those regions are suspected of being carcinogens). Similarly, polynuclear compounds, to many of which man is exposed, are potent skin carcinogens in mice, and induce lung cancer when implanted in the lungs of hamsters, but are quite ineffective on rat skin and completely inactive in guinea pigs. Aromatic amines induce bladder tumors in dogs and hamsters, as well as in man, but do not induce bladder tumors in rats or guinea pigs or mice, and are very weakly carcinogenic or inactive in rats and guinea pigs. Among the nitrosamines, whose role in human cancer is suspected but not demonstrated, we see a great variety of response among species and organs to their carcinogenic action (12). While all species are more or less susceptible to the carcinogenic action of nitrosamines, rats appear to be more sensitive than mice, while hamsters and Guinea pigs are intermediate, although there are exceptions with specific nitrosamines. To give a few examples of differences in response, nitrosoheptamethyleneimine induces lung tumors in rats, but not in Syrian hamsters, in which it induces tumors of the forestomach. Nitrosododecamethyleneimine induces tumors of the glandular stomach in mice, but only liver tumors in rats. Nitroso-2,6-dimethylmorpholine gives rise to tumors of the esophagus in rats, to tumors of the pancreas (similar to the most common form of human pancreatic cancer) in Syrian hamsters, and to tumors of the liver in guinea pigs. These differences are, presumably, due to differences in metabolism of the compound and in physiology between the species, but we have no idea what these differences are, nor how we could predict the action of such a carcinogen in man. It might be inactive in man, but it would be unwise to assume that and there is no way in which the evidence could be obtained which would prove it." (Lijinsky, S. 19–20)

Dr. Roe (AIHC) was one of the few witnesses who did place emphasis on organ specificity for carcinogens although he appeared to agree that one cannot be sure that there is such a thing as organ-specificity among species or in any given species:

"Where agents predispose to cancer, more often than not they predispose to a particular form of the disease or to a closely-related group of cancers. Only occasionally does the same agent predispose to cancers of several different sites or kinds, or does the same agent predispose to one kind of cancer when exposure is by one route and to another kind of cancer when exposure is by a different route. Occasionally the same agent predisposes to one kind of cancer in one animal species and predominantly to another kind of cancer in another animal species. However, all these are the exceptions rather than the rule and, as indicated above, one should be cautious in the interpretation of data which suggest that exposure to an agent is associated with increased risk of cancer of a wide variety of kinds. For instance the suggestion that fluoridation of water is associated with generally increased risks of cancer in humans (Burk & Yiamouyiannis, 1975) was due to poor epidemiology and not to any effect of fluoride (Doll and Kinlen, 1977)." (Roe, S. 11).

However, Dr. Roe was making this point specifically to argue against the use of increases in total tumor incidence as evidence of carcinogenicity. Elsewhere Dr. Roe agreed with OSHA's general principle and proposed two other formulations or corollaries of it:

"(i) There can be no presumption that *any* human organ would be affected in the case of substances that predispose to tumor formation in an animal test.

"(ii) There can be no presumption that a substance that gives negative results in animal tests will not predispose to one or other form of cancer in man." (Roe, S. 87–88).

Finally, in *In Re Shell,* the EPA Administrator, in addressing the issue stated:

"Most carcinogens are also not organ-specific. In a survey by Dr. Tomatis of 58 compounds known to produce liver tumors in mice, 40 also induced tumors in a variety of other organs. Furthermore, chemically induced tumors in one species need not appear in the same organ in other species. Thus, a carcinogen which induces liver tumors in mice might, for example, produce mammary cancers in rats and lung tumors in men." (39 FR 37268)

The following additional observation of the EPA Administrator is also relevant:

"Some witnesses also suggested that carcinogens can be species-specific—that is, a chemical substance might affect mice but not any other species, including man. This is theoretically possible. But of the thousands of compounds tested the record indicates that this effect has been suggested for only one of them, and even this single exception has been seriously challenged. I therefore will rely on the conclusion of such organizations as the International Association for Research on Cancer, which have rejected species-specificity as unsubstantiated.

"If carcinogens are not species-specific, it logically follows that the demonstration of carcinogenic effect in more than one species is not absolutely necessary for a finding of carcinogenicity." (39 FR 37269)

c. OSHA's Conclusions

Accordingly, while noting the divergence of opinion with regard to the mouse, and particularly to the mouse liver, discussed above, OSHA concludes that its proposed position is fully justified by substantial scientific evidence presented in this Record. OSHA concludes that the organs and tissues that are the targets of carcinogenicity may vary greatly in different species and even under different exposure conditions. Examples are known both of widely different target sites (e.g. benzidine induces bladder carcinomas in humans and cholangiomas and liver cell carcinomas in hamsters and rats) and of similar responses (e.g. vinyl chloride induces the same type of angiosarcomas of the liver in humans, rats, and mice). Thus, because no direct analogy of morphologic response can be expected from a carcinogen in test animals of different species and in humans, OSHA believes that it is appropriate and prudent to assume that target sites for carcinogenic action of a substance in humans are not necessarily the same as those found in animal experiments. Thus, satisfactory documentation of a "non-positive effect" in humans cannot be limited to the organs in which tumors have been induced in experimental animals.

5. Statistical Significance

a. OSHA's Proposal

The relevant portion of the proposed definition of "potential occupational carcinogen" was "any toxic substance which (1) causes, at any level of exposure or dose, . . . an increased incidence of benign or malignant neoplasms, or a combination thereof, in (i) humans or (ii) in one or more experimental mammalian species or (2) in a statistically significant manner decreases the latent period between exposure and onset of neoplasm in humans or in one or more experimental mammalian species" (42 FR 54184). Although this definition was not a model of clarity, OSHA had intended that evaluation for statistical significance would generally be carried out as part of the determination that a substance "causes" an increased incidence of neoplasms. This point was discussed

briefly in the Preamble however and OSHA believes the discussion made clear the intent:

For adequate demonstration of carcinogenicity of a substance in test animals, it is generally necessary that the increased incidence of neoplasms in one or more of the experimental groups should be evaluated statistically for significance (NCAB Report, p. 5; Mrak Commission Report, p. 465). This requires that the size of the experimental groups be adequately large to permit statistical evaluation (Mrak Commission Report, p. 465; UICC 1969, p. 17). (42 FR 54162)

In any event, as discussed below, OSHA agrees with the comments that statistical significance, in general, should be required.

b. The Public's Response and OSHA's Evaluation

Only a limited number of witnesses commented on statistical aspects of evaluation of carcinogenesis bioassays, and only a few technical papers were introduced into the Record (Fears *et al.*, 1977; Peto, 1974). Indeed, all participants agreed that statistical significance, in general, was required for treating a substance as a Category I potential carcinogen. Except for a few witnesses who pointed out the ambiguity in OSHA's proposed definition, most of the comments addressed two points: (i) whether criteria should be specified for the determination of "significance". and (ii) the frequency of occurrence of false positives and false negatives in carcinogenesis bioassays if specific criteria are adopted.

The following is a sample of comments presented in the Record criticising OSHA's proposed position:

"OSHA's proposed reliance upon test results that lack statistical significance is scientifically unsound. In written statements and oral testimony, the importance of statistical significance as an element to be considered in the overall evaluation of test results was emphasized time and again. For example, Dr. Umberto Saffiotti stated that 'statistical significance is a very important component of the judgmental activity . . .'" (Tr. 907)

Similarly, Dr. Donald Kennedy, Commissioner of Food and Drugs, indicated that he would require statistical significance in test results before labeling a component as carcinogenic. (Tr. 563) Dr. Arthur C. Upton, Director of the National Cancer Institute, agreed, noting that statistical significance is a necessary, but not in itself sufficient, basis for reaching scientific conclusions. According to Dr. Upton, test results should be significant not only in the statistical sense but also in light of an "adequate overall scientific evaluation."[144]

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"Thus, statistical significance is an essential aspect of scientific validity, and, when regulatory decisions are to turn on the statistical significance of experimental results, the term should not be left undefined.[145] Edward J. Baier recommended on behalf of NIOSH that statistical significance be defined at the 95% confidence level.[146] We believe that it should be defined at least at that level, although, if the recommendation of Dr. Richard Peto is accepted, even test results at the 95% confidence level "should not in general be taken as strong evidence that [the] substance is carcinogenic." (Tr. 2517) (American Iron and Steel Institute, Post-hearing Brief, pp. 86–88)

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"AIHC urges OSHA on the basis of this record to include statistical significance in its proposed criteria for the conduct and evaluation of animal and human studies. Whether or not a single common level of confidence should be selected in advance for all studies is controversial. Thus, NIOSH recommends that "statistically significant" be defined as "at the 95% confidence level" without any distinction as to the use to be made of an evaluation at that level of confidence. (NIOSH S. 5) Dr. Peto, on the other hand, testified that significance levels of .05 (95% confidence level) should not be taken as strong evidence of carcinogenicity. (Tr. 2517)

"It is AIHC's view that it is not only important to retain the concept of statistical significance; it is also important to recognize that the level of statistical significance selected for a particular evaluation depends on the use to be made of data. If the 95% level such as NIOSH recommended were to be selected by OSHA, OSHA should recognize three points relevant to that selection:

(i) Since 1/20 of the tests may be random false positives under this confidence criterion (Dr. Peto Tr. 2548), confirmatory evidence becomes a matter of prime importance.

(ii) There will be circumstances where a much higher level of confidence is required, as is discussed in a succeeding section of this brief. See *infra*, at 163–164.

(iii) Different levels of statistical significance may be relevant in evaluating an experiment which produces rare tumors as distinguished from one which induces an increase in the tumors to which a tumor prone species is subject.

"Dr. Upton made clear that statistical significance is not solely reliance on a bare arithmetic concept. We need to know also, he said, whether the controls behaved in accordance with the characteristics of the strain (Tr. 284); and the test results must be significant in light of the overall scientific evaluation of the test. *Id.* As Dr. Shimkin notes '[s]tatistics must make biological sense first and not be a mathematical exercise.' (Report of the NCI Clearinghouse at 74, AIHC P.H)." (AIHC Post-hearing Brief, pp. 142–144)

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"Data that is not statistically significant not only does not demonstrate carcinogenicity, but may not even give rise to a suggestion in which any scientific confidence can be placed. In short, the term 'suggestive' as used in the regulation is far too imprecise. As Drs. Snyder and Triolo point out, OSHA must define the level at which data will be deemed to be statistically significant as well as the level, below statistical significance, that will be deemed sufficient to warrant further regulatory action." (American Iron and Steel Institute, S. 8–9)

* * * * *

"Parameters of statistical significance have been established and these must be more thoroughly addressed in classifying substances. The mere statement that data should be statistically significant, as it appears in the Notice of Proposed Rulemaking, is insufficient. In a recent editorial published in Lancet II, September 1977, the authors concluded: in general, epidemiologists are familiar with the dangers (and the temptations) of drawing conclusions from findings in subgroups when total results are not significantly different from expected. (16) The referenced study by Howe, et al., found no significance between the incidence of cancer and the whole group of cases versus the controls. When the groups were broken down by sex, males evidenced a higher incidence than controls; females had a lower incidence than controls." (National Paint and Coating Association, S. 15–16)

Several comments reflected some confusion about the reasons why statistical analysis is undertaken, and about the concept of statistical "significance". The scientific reason for conducting statistical analysis of experimental results is to obtain an objective estimate of the possibility that an observed result might have arisen by chance. Conventionally, a level of probability is selected below which scientists agree that a result is statistically significant. However, such levels are somewhat arbitrary and for purposes of public policy additional considerations may be important, especially when the statistical analysis indicates marginal significance or the experimental system is insensitive.

Statistics are an important tool in evaluating carcinogenesis bioassays, but it should also be recognized that there are limitations inherent in these bioassays which require that additional scientific judgment be applied in evaluating these tests. Dr. Arthur Upton (Director, NCI) indicated in his testimony that in addition to considering statistically significant results, the tests should be ". . . significant in the light of adequate overall scientific evaluation" (Upton, Tr. 285). Dr. Umberto Saffiotti (NCI) agreed in his testimony, stating:

". . . statistical significance is an important component of the judgment, but by no means the only and exclusive method in the absence of any evaluation of the nature of the data. There is a biological evaluation [also] . . ." (Saffiotti, Tr. 898)

In using standard statistical procedures to evaluate the endpoint in a carcinogen bioassay, one can occasionally obtain false positive or

false negative results. It is important to keep the number of both false positive and false negative results as low as possible:

"The pool of chemicals under consideration by such a screening program must, of necessity, contain many useful nontumorigens as well as a few tumorigens. Thus, a screen must have good sensitivity since failure to classify correctly a tumorigen would be serious (a false negative), and a screen must have good specificity since there is loss to society if a safe, useful material is declared a tumorigen (a false positive)". (Fears *et al.*, 1977, p. 1941; Exhibit 5 to Griesemer Statement)

False negatives can occur for several reasons. These include the following:

(1) Early deaths due to such factors as excess toxicity or intercurrent disease in the treated animals such that there is not adequate time for expression of a carcinogenic response. These factors are detected by a biological evaluation of the overall study.

(2) The increase in the incidence of a tumor due to the substance is such that it cannot be detected statistically due to the spontaneous tumor rate at a specific site. An extreme example of this is that if the incidence rate of a tumor is 90% in the control population, it would be virtually impossible to detect a carcinogenic response at the site unless these tumors appear very early (decreased latency). At lower spontaneous tumor rates, strong carcinogenic effects can be detected but weak ones may still be missed.

(3) The incidence of a tumor is zero in the matched controls of the experiment and the numbers present in the treated animals are below those required for statistical significance. In order to evaluate such cases, one must have some knowledge of the incidence rate of that tumor in historical controls of the same species, strain and sex, preferably at the same laboratory. One must know whether this is a tumor which is indeed rare in a large historical control population or whether it is a tumor which occurs in low numbers but with a variable incidence in individual control groups. In the former case, a rare tumor, the presence of only a few tumors in the treated groups is of importance in determining the carcinogenic potential of a substance. In such a case, it can be shown that the matched control population does conform to the historical control data and that it is improbable that the number of tumors present in the treated group is due to chance. In the latter instance, the matched controls do not conform to the historical control population and the tumors seen in the treated animals could be due to chance.

False positive results can also occur:

"Tissue sites with high spontaneous tumor rates are more likely to yield false-positive results than are sites with low spontaneous tumor rates." (Fears *et al.*, 1977, p. 1944; Exhibit 5 to Griesemer Statement)

At those sites with a moderate to high spontaneous tumor rate, there is some degree of variability in the incidence between control groups. This variability is minimized in inbred strains of animals (Heston, S. 3–4), but still exists. If one has a large historical control population which can be broken down by individual control groups, one can determine the range of the variation in incidence for a tumor at a specific site. If in an individual bioassay, the incidence in the control group was at the lower end of the range and the incidence in the treated group was at the upper end, a false positive might result. However, by knowing the range of variation for a specific tumor site, such false positives can be eliminated. An example of the use of historical control data to verify that a positive result is biologically significant was given in the testimony of Dr. Richard Griesemer (NCI) (S. 9–10).

Positive results in one species, one sex and one dose level at a site with a high spontaneous tumor rate are those most likely to be false positive. The presence of a dose-response relationship, positive results at more than one site or in more than one species or sex all provide corroborative evidence that a carcinogenic effect is real and not a false positive (Fears *et al.*, 1944–45).

In summary, although a statistically significant increase in tumors at a tissue site is important in determining whether a substance is a carcinogen, other factors must be taken into consideration. Several witnesses discussed this point:

In an evaluation of the animal carcinogenicity test, we must judge whether the results are negative, positive, or inconclusive. This judgment must depend not only upon statistical analysis but upon expert experience and knowledge of laboratory animal disease and pathology. Proper randomization of animals, adequate and uniform pathologic sampling, and uniform pathologic interpretations are but a few of the critical areas that can alter experimental results. In some cases attention must also be given to the incidence, variability, and biological features of neoplasms in historical as well as matched control animals when possible treatment-related effects are assessed, although statistical analysis has not traditionally considered such historic data. (Squire, S. 13)

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It needs to be emphasized that the NCI bioassays, like any other well-designed cancer test, are interpreted continuously and carefully. A chemical is not labelled as a carcinogen automatically if it causes a statistically significant increase in tumors at one site in one species. If an increase is observed, the experiment is reviewed thoroughly, including consideration of the etiology of the tumor type, its occurrence in untreated controls in other experiments, dose-response relationship, etc. Many experiments raise specific problems of interpretation; the resolution of these problems requires evaluation by experienced professionals in several disciplines, and cannot be reduced to a formula. (Upton, S. 12)

Dr. Umberto Saffiotti (NCI) provided a thoughtful discussion of the factors involved in establishing causation in experimental biology, to which OSHA agrees, *viz*:

Let us try to understand what is involved in the concept of causation in the recognition of carcinogenic effects. In life sciences, "causation" implies an inference of sufficient condition to bring about a temporal sequential relationship between two events. In the case of carcinogens, the two events are the exposure of an organism to a given agent and the induction in that organism of a neoplasm. Studies on the concept of causation in biology emphasize its aspect of inference from a limited number of observations and therefore its inherent element of probability (Russel, 1948). Determining that an agent is capable of causing a given neoplastic response is the outcome of a complex judgmental activity, involving evaluation of many different factors, such as knowledge of the chemical and biological systems under consideration, determination of adequacy of the conditions of observation, qualitative and quantitative evaluation of the morphology and function of the observed organisms and their target tissues.

A judgment of causality in carcinogenesis may be based not only on the recognition of an excessive number of neoplasms in the exposed subjects but also on other factors, such as the observation of a pattern of pre-neoplastic and neoplastic lesions in a logical temporal sequence, information about the transport of etiologic agent to the target cells, and knowledge about its chemical reactivity. The judgment will derive from a multiplicity of direct and indirect observations which combine with general knowledge of the phenomena under study in the mind of the expert who is making this judgment. In this respect this process is similar to that of a physician diagnosing a disease from a multiplicity of observations and their logical analysis. A chemical agent should not be judged carcinogenic solely on the basis of a cursory "tumor count", without thorough evaluation of the conditions of exposure and of host response. A simple tumor count however, if markedly abnormal, can raise a considerable level of suspicion. Concurrence and reproducibility of the observations are important elements for this assessment. The judgment of causality also includes a consideration of possible interfering factors which may produce false appearances of cause-effect relationship, such as the presence of highly carcinogenic impurities in

a test substance, or—on the other side—the presence of intercurrent diseases in the test animal which may prevent the manifestation of a neoplastic response.

The judgment of carcinogenicity needs to be made by competent, experienced and objective professionals after analysis of all the relevant evidence. It goes without saying that this judgment should be objective and immune from conflicts of interest. (Saffiotti S. 6–7)

Several witnesses were asked whether OSHA should specify a level of probability below which results would be regarded as statistically significant. NIOSH proposed that OSHA should define "statistically significant" as "at the 95% confidence level" (S. 5). However, Dr. Donald Kennedy (Commissioner, FDA) expressed the opinion that such a specification could not be useful:

"The purpose of the test of statistical significance is to assure the experimenter and his or her scientific referees that the result that has been obtained, that is, the difference between experimentals and controls, is unlikely to be due to chance alone.

"Q: Do you think it would be useful of OSHA to set forth in the regulation the minimum level of statistical significance that it requires in one of the animal tests that is going to be used as a basis for regulation?

"A: No, because as I think I see within the universe of animal testing enough variation in the kinds of experiments done, and thereby in the confidence limits and levels of statistical significance that one would want to assume, that I am not sure that such a prescription wouldn't prove to be more confining than it is helpful. (Kennedy, Tr. 564)

Mr. Richard Peto (Oxford University) recommended that OSHA should use a specific procedure for statistical evaluation and should set a stringent standard for statistical significance:

"As with humans, so also most animal cancer incidence rates rise steeply with the age of the animal. Thus, the number of cancers produced in an experiment can depend critically on the numbers of animals that survive into old age. All sorts of irrelevant aspects of animal management and treatment toxicity can affect the pattern of survival of groups of experimental animals and hence the number of cancers observed. Because of this, misleading conclusions may well emerge from an animal experiment unless due allowance for intercurrent death rates is made during the statistical analysis. Straightforward ways of making such allowances are listed in Annex F, and it is recommended that these methods (or some other statistical methods which correct validly for the effects of mortality on cancer yields in experimental animals) be routinely used in the proposed evaluation by OSHA of animal carcinogenicity data.

"Because in most experiments animals of both sexes and of more than one strain are studied, and the separate incidence of tumours at each of a dozen or more anatomical sites is independently documented, some of the many significant levels calculated will probably be less than 0.05 just by chance. Because of this, individual P-values of 0.05 (or even 0.01) are not necessarily convincing unless the effects concerned can be reproduced in independent experiments or unless the agents concerned show striking activity in a battery of short-term tests; for a single animal experiment to be convincing without such support, a P-value of well under 0.01 (perhaps even 0.001) should usually be required. Unless this policy of requiring rather extreme P-values is adopted, an unacceptably large number of misleading results will emerge by chance alone." (Peto, S. 16–17)

Mr. Peto's first suggestion, that OSHA should use a standard and sophisticated method for analyzing bioassay results, is not always practical because OSHA is necessarily limited to interpreting results of experiments conducted in the past, for which the required data are frequently not available. His second suggestion, to use a stringent criterion for signifiance, is addressed to the problem of avoiding false positives in an experiment involving multiple comparisons. This problem was also posed in a paper by Salsburg (1977), but Salsburg's conclusion that false-positive rates are likely to be high was challenged by Fears and Tarone (1977). The problem was analyzed in some detail in another paper by Fears *et al.* (1977), who showed that false-positive rates are likely to be significant only at sites where the spontaneous incidence of tumors is high. Using data on spontaneous incidences of tumors in the NCI bioassay program, they calculated that the false-positive rate would be less than 0.025 (1 in 40) if a requirement were adopted that tumor incidence should be increased significantly at the $p=0.05$ level at both dose-levels in the same species. Fears *et al.* (1977) pointed out that the adoption of stringent criteria to minimize the false-positive rate would result in an increase in the false-negative rate. Accordingly some judicious trade-off between the two is required:

"The tissue site at which a significant result is found can be of considerable importance in a chemical screen. Tissue sites with high spontaneous tumor rates are more likely to yield false-positive results than are sites with low spontaneous tumor rates. For example, in the pituitary gland of the female Fischer 344 rat, the probability of a false positive in either of 2 dose groups is 0.059 and the probability of a false positive at both dose groups is 0.007. In contrast, for the majority of tissue sites (those with spontaneous tumor rates of less than 1%), the probability of a false positive in either of 2 dose groups is 0.00018. Thus, a significant result (even at only 1 dose) at a tissue site with a low spontaneous tumor rate offers strong evidence against the chemical under study. The presence of a dose-response relationship (higher tumor rates at higher doses) provides corroborative evidence of tumorigenicity.

"The upper bounds on the misclassification rates for the decision rules considered in this paper offer valuable insight into the problems of chemical screening. The upper bounds for the strategy that indicates a positive compound if a significant result is found in either dose should serve as a warning against a screen that relies solely upon statistical significance and does not require biological consistency. The complex 2-species, 2-sex screen described previously which requires the supporting evidence of significance in both dose levels yields an acceptable false positive probability. This lower false positive error rate is accompanied by a higher probability of a false-negative result. Of course, there are other biologically consistent results that should be considered as evidence of tumorigenicity, such as the occurrence of a significant result in 1 dose for both male mice and male rats at the same tissue site. A good screen must incorporate biological knowledge and careful statistical analysis." (Fears *et al.*, 1977, p. 1944; Exhibit 5 to Griesemer Statement)

And, the OSTP Staff Paper of February 1979 briefly discussed this issue:

The various testing methods discussed above cannot provide a simple yes or no answer regarding the potential for human carcinogenesis. Rather, test results offer a probability that such a potential exists. In evaluating any such test, one examines the data and then performs a statistical test of the null hypothesis—that there is no difference between the control and experimental groups in cancer (or mutation) rate. If there is, indeed, a difference, the statistical test will provide a probability that such a difference could have been observed due to chance alone. This probability is expressed as a p value. The statement that a test is "significant at a p value of less than 0.05" means that, if the null hypothesis were true (*i.e.*, if there were no actual difference between the control and the experimental groups), then there would be less than a 5% probability that such a difference could have been observed due to chance alone.

By convention, scientists often choose a p value of less than 0.05 as "statistical proof" that the null hypothesis is false. However, any given p value on a single test must be viewed in the context of other available data. For example, if a sufficient number of tests is performed, predictably a "statistically significant" difference will be found in at least one test, regardless of the p value which is chosen, simply as a result of random variation. (OSTP, 1979, pp. 12–13).

c. OSHA's Conclusions

On reviewing the Record, OSHA concludes that statistical analysis is an important tool in the evaluation of results of carcinogenesis bioassays, in that it permits the objective testing of hypotheses and the determination of the probability that certain observed results

might have been obtained by chance. Nevertheless, OSHA concurs with the statements of numerous witnesses that evaluations of bioassays cannot be based on statistical analysis taken alone, but requires a scientific evaluation of all aspects of the experiments. OSHA also concludes that while it may not be possible to set a specific criterion for statistical significance that can be applied uniformly in all circumstances (i.e. the degree of statistical significance that is observed must be evaluated with reference to the spontaneous tumor incidence at the site in question), such issue is obviously a factor in the determination of causality. In this respect, OSHA places considerable weight on the detailed analysis of the problem by Fears *et al.* (1977). For further discussion, see *"Confirmation of Results"*, section V.D. 9 below. Thus the final set of regulations states at 1990.143(j):

"(j) *Statistical Evaluation.* Statistical evaluation will be used in the determination of whether results in human, animal or short-term studies provide positive evidence for carcinogenicity, but will not be the exclusive means for such evaluation."

6. How Much Weight Should Be Placed Upon the Induction of Benign Tumors in Animals as an Indication of Potential Carcinogenic Hazards in Humans?

a. OSHA's Proposal

In the preamble to the proposed regulations, OSHA proposed to place as much weight on an experiment in which only benign tumors are observed, as upon experiments in which both malignant and benign tumors are induced. OSHA recognized that this issue has been controversial in the past and discussed the issue at some length in the preamble to the proposal. OSHA concluded:

"It is plain from the above quotations that the scientific discussion is not concerned with the significance of benign tumors, but rather with the precise degree of weight that should be placed upon the results of an experiment in which a substance induces only tumors that are authoritatively classified as benign in the test animals. Since such instances are acknowledged to be rare [citations omitted], the issue may be somewhat academic. (42 FR 54163)

b. The Public's Response and OSHA's Evaluation

At the outset, it should be clear that the issue raised in this section was not, as some witnesses seemed to suggest, whether substances which induce benign tumors in animal experiments are of little concern because they are expected to induce "only" benign tumors in humans also. Rather, the issue was whether the induction of benign tumors in animals is a manifestation of carcinogenic activity of a substance, which might be manifested as the induction of either benign or malignant tumors (or both) in other species, including humans. The latter was the singular issue—and because no one presented a case of a substance that produced only benign tumors—a highly academic issue.

Many witnesses testified and offered a wide range of opinions on this issue and it appeared that there was substantial evidence and agreement in the Record that the issue is indeed academic. Dr. Umberto Saffiotti (NCI) testified that:

"In 25 years of work in chemical carcinogenesis, I am among those who are not able to come up with a good documentation of any kind that substantiates the mechanism for the induction of benign tumors alone that would never progress to a more advanced stage." (Saffiotti, Tr. 878)

Dr. Saffiotti's testimony was supported by Dr. Richard R. Griesemer (NCI) who stated that, in his opinion, there were no such things as benign tumors in chemical carcinogenesis experiments (Griesemer, Tr. 877–78). Dr. Curtis C. Harris (NCI) also testified that he knew of no chemical that caused only benign tumors (Harris, Tr. 2012), and Dr. Nathan Dubin, (Medical College of Pennsylvania) concurred with this opinion (Dubin, Tr. 1210).

Furthermore, when asked if he had ever dealt with a substance that induced only benign tumors in test animals, Dr. Benjamin Trump, (Univ. of Maryland) testified:

"Never. In all of the examples that we have worked with, what used to be or what some people might have called benign lesions years ago are clearly part of the progression from normal to malignant, and often as in the case of the work that we have done with kidney carcinomas . . . (t)hey are tiny carcinomas, not benign adenomas as they used to be called, because they can be transplanted . . . I think the term "benign tumor" is a dangerous concept, because benign tumors in the human, such as leiomyomas of the uterus, classically called benign tumors, can undergo malignant degeneration. In experimental animals the so-called benign tumors I regard as earlier forms, and often just miniature versions.

"Furthermore, since we cannot predict the organs in which tumors may occur in humans from a compound tested, from the organs in the test animal, even if there was a benign tumor in the brain it is not a very desirable thing to have since it kills the host. So for all of those reasons, I think that concept has become outmoded." (Trump, Tr. 2011–2012)

In addition to this testimony, Dr. Harold L. Stewart, who was head of pathology at the National Cancer Institute for thirty years, also testified at the hearing. Dr. Stewart was instrumental in organizing the National Institutes of Health's Registry of Experimental Cancers, which the World Health Organization has designated the International Reference Center for tumors in laboratory animals (Stewart Tr. 696). Under questioning he testified that in his opinion there is no benign epithelial tumor of the liver in rodents, and that he had never seen benign tumors of the thyroid, pituitary or adrenal glands in rodents (Tr. 678–680).*

Dr. Saffiotti (NCI) took the position that even if a substance were found to induce only benign neoplasms in a test animal species, it would not necessarily have the same effect in other species, including humans. He stated:

". . . we know that carcinogens in general can act on different types of cells, tissues and organs in different species. They could therefore induce a neoplastic response in a target cell type capable only of giving rise to benign proliferation in one species, while hitting a cell capable of developing into a malignant neoplasm in another species. We have no evidence now that such selective mechanisms exist for the induction of exclusively benign neoplasms." (Saffiotti, S. 17)

Dr. Saffiotti discussed two other types of results from carcinogenesis experiments. The first is the case where we have the induction of only neoplasms which are diagnosed as benign "but which belong to a type known to be capable of progression to a malignant state" (S. 17). Examples listed by Dr. Saffiotti included lung adenomas and hepatomas of the liver. With respect to these kinds of lesions, Dr. Saffiotti pointed out that it is very difficult to rule out invasion or metastatic spread of a particular tumor, without an extremely detailed examination of the animal's tissues (Saffiotti, S. 18). In cases such as this, Dr. Saffiotti stated:

"(t)he prudent policy approach . . . is to assume that their malignant potential may be likely to occur in other biological conditions, such as in extrapolation to humans. (Saffiotti, S. 17).

The other case which Dr. Saffiotti considered was one in which most of the induced neoplasms are benign, but in which a relatively small number of tumors have already progressed to the malignant state. Dr. Saffiotti concluded with respect to such cases:

". . . Although the number of tumors diagnosed as malignant may not reach

*The question of the significance of the induction of liver tumors in mice and their development to malignancy was dealt with at length in Section V.D. 1.

statistical significance as such in the number of animals at risk, the total neoplastic response (benign and malignant) may be clearly significant. In such cases the arguments given above for inclusion of neoplasms diagnosed as benign in a total neoplastic response are further reinforced by the presence of clearly malignant cases." (Saffiotti, S. 18–19)

In one of the exhibits to his written testimony, Dr. Stewart addressed the significance of the biological process of tumor growth in humans:

"In the sphere of clinical medicine, the terms 'benign' and 'malignant' are useful. They are part of the language by which pathologists and surgeons communicate. For practical purposes, the differential diagnosis of cancer depends on aspects of abnormality of nuclei, mitotic figures, and growth patterns. Let us consider two patients each with a nodule in the thyroid gland. The nodule in patient one has a follicular pattern and is confined to the gland. The diagnosis is benign adenoma. The treatment is a simple excision. In patient two, the nodule exhibits essentially the same follicular pattern, but the growth has broken through the capsule of the gland and penetrated the veins. The diagnosis is cancer. Treatment requires wide local excision and deep neck dissection, with all of the complications, morbidity, and mutilation that attend this surgical procedure. Thus, the terms 'benign' and 'malignant' are clinically useful. Nonetheless, from a strictly biologic point of view, the neoplasms of these respective patients are of the same order. They differ only by the degree of their progression. Had patient one delayed treatment, the tumor could have progressed to the stage observed in patient two. Conversely, had patient two sought treatment earlier, the tumor may not have progressed beyond the stage observed in patient one. With cancer, events often, though not necessarily, occur in irreversible succession." (Stewart, 1977, p. 308; Exhibit C to Stewart Statement)

Dr. Robert Squire, (Johns Hopkins Univ.) provided an analysis of the issue of the biology of tumor induction in animals. Dr. Squire explained that neoplasia is a pathological process and not a class of static pathological states that may definitively be classified as benign or malignant. He stated:

"Since the goal of carcinogenicity testing in animals is to assess potential for neoplastic induction, in all of its stages, the process, not simply the final stages of malignancy, must be evaluated. In a pathological evaluation of an animal carcinogenesis test, the determination of specific tumor incidences requires that, unless there is evidence to the contrary, all neoplasms of the same cell type be considered together. It is the responsibility of the pathologist to indicate which tumor types represent sequences in the same neoplastic process and to combine them for statistical analysis." (Squire, S. 18)

As Dr. Stewart stated in another one of his exhibits:

"Some experimental pathologists have forgotten, while others never learned, that the field of human oncology has many examples of cancers, some that arise as innocent-looking lesions, others that pursue an indolent course over a long period of years and metastasize infrequently late in the disease, and still others so well differentiated that when sections of the metastases are placed side by side with a section of the organ of origin the two may not be distinguishable. Cancer of the urinary bladder arises in man as an innocent-looking papillary structure which, if left untreated, grows into the lumen and into the wall of the bladder and metastasizes widely, the metastases taking on the appearance of a highly malignant transitional-cell or undifferentiated-cell carcinoma. A classic example of a human tumor that may metastasize while still retaining the appearance of the organ of origin is thyroid gland cancer, formerly miscalled benign metastasizing goiter. There are additional examples of cancers in human medicine that never metastasize, such as the gliomas and basal cell carcinomas. Examples of those that persist at the site of origin for a long period of time and metastasize late in the disease and then only in a fraction of the cases, but are nevertheless malignant and lethal, are certain fibrosarcomas, leiomyosarcomas, and salivary gland tumors. It is often difficult for the clinical pathologist to distinguish between those salivary gland tumors classified as papillary cystadenoma and papillary cystadenocarcinoma, since tumors with a relatively benign histological appearance may metastasize after a long period of slow growth. Similarly, a mixed tumor of the salivary glands may after a long static period undergo rapid growth and metastasize widely. The late Dr. Joseph McFarland (1943) used to refer to this phenomenon as a ripening process of the mixed salivary gland tumor. There are thus no immutable criteria by which one can, with certainty, diagnose all cancers during all stages of their progression from their early inception to their terminal metastasis. One needs to understand very well the tumor with which he is dealing, its histological appearances, and its biological behavior at different stages of its growth. The phenomenon of tumor progression is inadequately understood in comparative pathology." (Stewart, 1975, p. 310; Exhibit B to Stewart Statement)

Under questioning Dr. Stewart gave other examples of this biological progression. He testified that the alveologenic tumor of the lung in mice had been studied by intermittent sacrifice of the test animals and that:

"We could trace that tumor from the moment it just formed a few cells in an alveolus. Then it became larger. Then it invaded adjacent alveoli. Then it invaded the bronchus . . . [t]hey metastasize in a certain number of cases. They spread to different organs of the body. That tumor is malignant from day one. It is a malignant neoplasm. . . . [t]hat is a malignant tumor from the very beginning." (Tr. 635)

The testimony of the above witnesses, along with that of Dr. Samuel S. Epstein (Univ. of Illinois) (Epstein, 1978, p. 2430 Exhibit 10c to Epstein Statement) and Dr. Richard Bates (NIEHS; FDA) (S. 19–21) provided strong support for OSHA's judgment expressed in the Preamble to the proposed regulation, that the induction of benign or malignant tumors should have synonymous implications with respect to human health. As Dr. Bates testified:

"Q. So for practical purposes you would accept the induction of benign neoplasia as posing the identical risk as something that induces malignant neoplasia in a test animal?"

"A. I would say that they pose a human risk and I cannot distinguish between the two of them in terms of their potency for humans." (Bates, Tr. 661)

Several witnesses disagreed that equal weight should be attributed to the induction of benign and malignant tumors. Dr. Bernard Weinstein (Columbia University) concurred with the cautious opinion expressed by the 1977 National Cancer Advisory Board Subcommittee, of which he was a member. The Subcommittee Report stated:

"The occurrence of benign neoplasms raises the strong possibility that the agent in question is also carcinogenic since compounds that induce benign neoplasms frequently induce malignant neoplasms. In addition, benign neoplasms may be an early stage in a multi-step carcinogenic process and they may progress to malignant neoplasms; also, benign neoplasms may themselves jeopardize the health and life of the host. For these reasons, if a substance is found to induce benign neoplasms in experimental animals it should be considered a potential human health hazard which requires further evaluation. In experiments where the increased incidence of malignant neoplasms in the treated group is of questionable significance, a parallel increase in incidence of benign tumors in the same tissue adds weight to the evidence for carcinogenicity of the test substance." (NCAB 1977, p. 462, Exhibit B to Weinstein Statement)

Dr. Weinstein testified:

"Unlike OSHA, I would not place as much weight on an experiment in which only benign tumors are observed. . . . While there is a respectable body of scientific opinion which supports the OSHA position, I would classify a compound which truly produces only benign tumors as a suspect carcinogen which should have high priority for further testing. However, in animal bioassays where a substance is found to induce primarily benign tumors in certain tissues, and there are some malignancies in these same tissues, then I would more readily classify the compound as a carcinogen." (Weinstein, S. 3–4)

Dr. Paul M. Newberne and Dr. Adrianne Rogers (MIT) agreed that the phenomenon of induction of only benign tumors is an "unlikely event" (S. 17), but did not agree that a general rule equating the induction of benign and malignant tumors was appropriate. They summarized their position as follows:

"Our understanding of mechanisms of carcinogenesis does not permit us to make generalizations about the relationship between induction of benign and malignant tumors or between development of spontaneous and induced tumors. Clearly there are benign tumors which are not precursors of malignant tumors or indicative of carcinogen exposure and others which are. At this point judgment of the significance of a given tumor must be based on knowledge of the behavior of that tumor in that animal species or strain. Benign tumors have little effect on the host aside from occupying space or by interfering mechanically with function while malignant tumors destroy the host unless removed or arrested. These two classifications are as valid in safety evaluation as they are in human or veterinary diagnostic pathology; they should be separated when interpreting animal safety data. Considering all tumors (benign or malignant) equally significant as indicators of carcinogen exposure will neither increase our understanding nor provide information on carcinogenic hazards." (Newberne and Rogers, S. 18–19)

In addition to these witnesses, Dr. Francis Roe (AIHC) submitted written comments stating that although he felt that the induction of benign tumors

". . . prompts the need for particularly stringent carcinogenicity tests . . . it is positively misleading to equate benign and malignant tumors. An agent which gives rise predominantly to malignant tumours must be regarded as *more hazardous* than one which under similar circumstances gives rise to only, or predominantly, benign tumors. The inescapable corollary of this is that an agent which predisposes only or mainly to benign tumor formation is *less hazardous.*" (Roe, S. 89)

Dr. Roe, in essence, urged OSHA to give priority in regulation to compounds which produced more obviously malignant tumors in animal test systems.

Dr. William Butler (NACA) also disagreed with OSHA's position and commented as follows:

"The arguments should not be used, as set out in the proposed rules, suggesting that benign neoplasm should be considered as important because it progresses to malignant neoplasm. The available evidence is against this suggestion. Most of the biological evidence of the behavior of neoplasm comes from man and from clinical experience, and it is evident that the vast majority of benign neoplasm do not progress to malignant and that malignant neoplasm does not develop from benign neoplasm. This is the current teaching in pathology (Anderson, 1971). It is further supported by the evidence in the rat (Williams, Klaiber, Parker and Farber, 1971). The statement, "(B)enign tumors are often pre-cursors of malignant tumors" has not been substantiated in practice. The correct approach in assessing the possible carcinogenicity of a test compound should be the accurate designation of the data, and a direct interpretation of this without reliance upon an intervening hypothesis of progression. The terminology to be used must necessarily be equally discriminating. By definition, a carcinogen induces malignant neoplasia, therefore, if a chemical agent induces just benign neoplasia, it should not be considered to be a carcinogen. Some other descriptive word is required. It is important to make such distinctions so that the underlying biology is clearly reflected in the terminology used to describe the phenomena." (Butler, S. 20–21)

The International Agency for Research on Cancer, in the latest revision of the preamble to its Monograph series, made the following statement:

"Many chemicals induce both benign and malignant tumours; few instances are recorded in which only benign neoplasms are induced by chemicals that have been studied extensively. Benign tumours may represent a stage in the evolution of a malignant neoplasm or they may be 'end points' which do not readily undergo transition to malignant neoplasms. If a substance is found to induce only benign neoplasms in experimental animals, the chemical should be suspected of being a carcinogen and requires further investigation". (IARC, 1978, vol. 17, p. 15)

The most extensive discussion of this issue in the Record was that of Dr. Robert Squire (Johns Hopkins Univ.):

"Evidence from animal studies has indicated that most epithelial cancer is a multistage process beginning with proliferative or dysplastic lesions and progressing through development phases to carcinoma (Farber 1976). The *Summary Statement* of the NCI Symposium "Early Lesions and the Development of Cancer" described the process:

"Data were presented at the Conference regarding the development of cancer of the urinary bladder, uterine cervix, liver, breast, skin, lung, colon, pancreas, and stomach. It is clear that the development of cancer in all of these organ sites is a prolonged process, which may take 20 years or more in humans to reach its invasive stages. Before invasive malignant disease occurs, various preneoplastic changes occur in all of the above organ sites. Although these preneoplastic changes have not been generally considered to be "cancerous" (in the classical, clinical diagnostic sense of the term), they are definitely an integral part of the process of development of cancer. Because the prognosis for invasive malignant disease becomes worse as the stage for the disease increases, it is essential that more intensive efforts be devoted to study of the disease process in its preneoplastic states (Anthony et al. 1976; see Appendix B).

"Before invasive cancer develops, many of the lesions exhibit the pathological features characteristic of benign neoplasms, as defined in standard pathology texts (Willis 1967, pp. 18–26). Under experimental conditions it has been determined that progression to malignancy is compound and dose-related and that it varies in individuals, strains, and species (Homburger 1974; Selikoff and Hammond 1975). The basis for the variations is not well understood, although it has been observed that genetics, hormonal factors, nutrition, age, route, and schedule of exposure are among the many factors that modify carcinogenic response. The effect of exposure is well illustrated in skin painting studies in mice, where effects may be either none, benign papillomas, or carcinomas, depending upon the dose of carcinogen applied (Stenback et al. 1974). The authors stated, "There is a direct relationship between dosage and degree of 'neoplastic potentialities,' if one can visualize a gradation from regressing papilloma through the growing benign tumor or to the invasive cancer" (p. 188).

"It would be incorrect of course to say that all preneoplastic or benign neoplastic lesions progress to cancer; many clearly do not. But it is misleading to consider those neoplasms that do not progress to malignancy as biologically distinct and unrelated to the carcinogenic stimulus. There is no reason to conclude that the failure of neoplasms to become malignant in one individual or species will predict the same behavior in other animals.

"The statement is often made that human cancers begin as malignant proliferations and do not develop from so-called benign precursors, as has been observed in experimental animals. This position, however, fails to recognize that interim observations of early lesions, which can be readily made in experimental animals, are rarely possible in humans. In fact, there are several cases in which early observations in humans have been possible, and these indicate that human cancer is preceded by benign-appearing proliferations that proceed through a sequence of neoplastic alterations similar to changes that occur in experimental animals. These cases include ones of bladder cancer, kidney cancer, pancreatic cancer, and liver angiosarcomas associated with exposure to vinyl chloride (Popper and Thomas 1975; Popper et al. 1977; Friedell 1976; Greene 1973; Reuber 1974; Heatfield et al 1977; Levitt et al. 1977). Chemically induced bladder cancer in experimental animals and man progresses through stages of noninvasive epithelial proliferation (hyperplasia) before invasive cancer develops (Jacobs et al. 1977; Squire et al. 1977; Ito 1969; Roe 1966). In his report on urinary bladder neoplastic changes in mice, Roe (p. 238) stated that:

'. . . we have been greatly impressed with the apparent gradation of lesions from simple hyperplasia and metaplasia, through benignity to malignancy. At times it was difficult to draw the line between one category of lesions and the next and we formed the strong impression that there is a tendency for the less proliferative lesions to progress to the more proliferative and for the benign to progress to the malignant.'

"In reporting a study of human bladder neoplasms, in which 100 cases were followed for 15 years or more, Greene *et al.* (1973, p. 207) stated:

'The most significant findings from our study are that 1) 73 percent of patients had recurrent tumors, 2) 22 percent had recurrent neoplasms that were less differentiated and more lethal than the original lesion and 3) 10 percent had frankly invasive carcinoma with diffuse metastasis that caused death. Somewhat similar findings were reported by Pyrah and associates, who noted recurrent tumors in 70 percent of patients and frank carcinoma in 13 percent. Such somber data imply that the original tumors cannot be considered benign papillomas but must be considered carcinomas and treated as such.'

"Hepatocellular carcinomas have also been identified as developing from so-called benign hepatic adenomas in women taking contraceptive steriods (Popper et al. 1977).

"Considering the similarities between neoplasms in humans and animals in other respects, I see little justification for presuming that man is unique with respect to neoplastic development.

"The terms 'benign' and 'malignant' have served the field of surgical pathology well, since they attempt to reflect a prognostic judgment on a given patient. They do not always, however, properly define the neoplastic process that, in a population of experimental animals, we take as evidence of exposure to a carcinogenic stimulus. Willis' well-known text, *Pathology of Tumors*, discusses the problem of tumor classification:

'Many histogenetic species of tumours include some growths which occupy the borderline between innocence and malignancy. Good examples of this are afforded by papillary epithelial growths, many of which cannot be classed with precision either as benign papillomas or malignant papillary carcinomas. Thus the papillary growths of the bladder exhibit a complete range of structure and behavior—from the slowly growing wholly superficial pedunculated villous papilloma of uniform fully organized architecture, to the rapidly growing, infiltrative, sessile, irregularly papillary carcinoma. Of many of the intermediate members of such a series, it is difficult to assess the degree of malignancy and to predict their probable course. Some growths, with a past history and microscopical structure which lead us to look upon them as 'benign,' may nevertheless prove their essential malignancy by later recurrence, infiltration or metastasis. Similar borderline characters are displayed by some of the papillary growths in the intestine, larynx, thyroid, breast, and in ovarian cysts (Willis 1967, p. 18).'

"In his conclusion, Willis (p. 26) stated further:

'Innocence' and 'malignancy' are not two distinct biological properties pertaining to neoplasms, but merely convenient terms which have become firmly entrenched in pathology because of their prognostic value. By experience of each histogenetic class of tumours, we have learnt which particular tumours in that class are likely to remain local in their growth and to be curable by local removal, and which ones will spread more or less widely and dangerously. The pathologist knows, however, that in most classes of tumours growths of intermediate behavior occur, for the prognosis of which the bald terms 'innocent' and 'malignant' must be qualified. Between the cellular characters of tumours and their degrees of malignancy there is a broad parallelism, largely based on the inverse relationship of rate of proliferation and degree of differentiation of tumour cells. To this parallelism, however, there are many exceptions.

'The notion that 'malignancy' implies something new and peculiar added to neoplasia is false. So also is the notion that there is a specific "malignant" cachexia.'

"All of these observations support the concept of neoplasia as a pathological process, not as static pathologic states that may definitively be classified as benign or malignant. Since the goal of carcinogenicity testing in animals is to assess potential for neoplastic induction, in all of its stages, the process, not simply the final stages of malignancy, must be evaluated. In a pathological evaluation of an animal carcinogenesis test, the determination of specific tumor incidences requires that, unless there is evidence to the contrary, all neoplasms of the same cell type be considered together. It is the responsibility of the pathologist to indicate which tumor types represent sequences in the same neoplastic process and to combine them for statistical analysis. (Squire, S. 14–18)

Dr. Bo Holmberg (Swedish NBOSH) testified as follows:

"When considering the problem of benign tumors in animals for the evaluation of the carcinogenic risk it should be recognized that benign tumors often appear earlier than malignant tumors in experimental systems (Holmberg *et al.*, 1976, Appendix 6). There are very few, if any, examples in which chemicals induce only benign tumors in mammals. Even the recognition of benign tumors is complicated in animals because the experimenter usually cannot observe the progressive development of tumors and must rely on histopathological evidence. Early stages of malignant tumors often appear benign and metastases may be difficult to detect. A classical case is the mouse hepatoma, which often appears benign unless the animal is allowed to live to extreme old age and the lungs are carefully searched for metastases.

"Should the formation of hepatomas in mice not be taken as an indication of carcinogenic activity, some compounds known to pose a carcinogenic risk to humans would not be classified as carcinogens. The human bladder carcinogen 2-naphthylamine, administered in the drinking water to outbred mice for 84 weeks (Clayson and Ashton, 1963) did for instance increase the incidence of hepatomas relative to that in controls. In newborn mice, which generally are considered to be more sensitive to carcinogens than adult animals, 2-naphthylamine induced lung adenomas, one hepatoma and one lymphosarcoma (Radomski *et al.*, 1971).

"To take another established carcinogen as an example, the human bladder carcinogen benzidine given to mice by subcutaneous administration (Prokofjeva, 1971; Bonser *et al.*, 1956) did also increase the frequency of hepatomas. Should histologically benign liver tumors in mice, appearing after exposure to chemical carcinogens, not be regarded as an indication of carcinogenic activity of the compound such substances as 2-naphthylamine and benzidine would escape classification. The conclusions drawn in the overview by Tomatis *et al.* (1973) on the biological effects of hepatomogenic compounds, make it more prudent to regard the appearance of hepatomas in the mouse as an indication of carcinogenic hazard to man." (Holmberg, S. 20–22)

Dr. Richard Bates (NIEHS; FDA) also presented a detailed discussion of the issue:

"Another debated issue is the significance of benign tumors as an index of carcinogenicity of a chemical. This subject has been debated by many groups of scientists who have issued recommendations on the interpretation of carcinogenicity studies. Depending upon which report is read, one will receive the advice either to base the assessment of carcinogenicity only on the presence of malignant tumors, ([38]) on both malignant and benign tumors, ([39]) or on both malignant and benign tumors when both are present in the same organ, but not on benign tumors when malignant tumors are not also present. ([40]) Thus, this is certainly an issue on which unanimity of scientific opinion does not prevail. In analyzing this issue it is helpful to consider the circumstances under which the distinction between benign and malignant tumors developed and how these apply to the problem of determining whether or not a chemical is capable of inducing cancer. These terms developed in the context of human medicine where the goal was to predict the likelihood that the tumor found in an individual patient would be lethal. It was noted that tumors with certain characteristics were most likely to be lethal, that is malignant, whereas others did not indicate a bad prognosis. Thus, the terms benign and malignant reflected the expected outcome of the presence of the tumor in the individual patient. They bore no relationship to the causal events leading to these tumors and whether or not such events would produce the same or a different kind of tumor in another individual. The guidelines for distinguishing between benign and malignant tumors are very good with some kinds of tumors, but relatively poor for others. Thus, in the latter case, disagreement may exist among qualified pathologists as to whether the tumor has passed from the point at which it is benign to that at which it is malignant. The sharp distinction between benign and malignant tumors is also somewhat muddied by the tendency of some kinds of benign tumors to progress onward to malignancy.

"In the experimental bioassay, we are not really interested in whether the tumor will or will not be lethal in the particular mouse or rat. We are interested in whether these tumors indicate that the chemical inducing them is capable of causing cancer under some circumstances in exposed human beings. Thus, the question is whether the

tumors represent an index of carcinogenicity of the chemical rather than whether they represent a lethal threat to the animal in which they reside. A number of experimental studies suggest the importance of considering the presence of benign tumors as an indicator that their inducing agent is capable of causing malignancy. The induction of benign adenomas of the mouse lung has been used as an indicator of carcinogenicity. It has been shown that many widely studied chemical carcinogens that are clearly capable of inducing malignancy under some circumstances cause an increase in this tumor type. ([41]) Some scientists discounted an early study showing the induction of benign tumors of the liver in mice by DDT ([42]) because no malignancies were found. These studies were stopped after 18 months. Subsequent studies lasting for a longer period confirmed this result and also showed the induction of some malignant tumors of the liver. ([43]) The induction of tumors of the mammary gland by x-ray and by carcinogenic polycyclic hydrocarbons has been extensively studied in rats. These carcinogenic agents are capable of inducing both malignant adenocarcinomas and benign fibroadenomas of the mammary gland. These tumors are similar to those found in the human breast, and in humans, as in the rat, the former is clearly malignant and the latter clearly benign. Studies in rats, however, have shown that the relative proportion of these two types of tumors that are induced varies markedly among different genetic strains of rat, ([44]) indicating the importance of genetics in determining whether a carcinogen will induce a benign or malignant tumor. Thus, it has been shown that under some experimental conditions chemicals capable of inducing malignancy will primarily induce benign tumors. It is not clear that there are any chemicals capable only of inducing benign tumors and never inducing malignancies, though the possibility that there may be some cannot be ruled out. As with many other questions, the regulator must make a decision before arguments have ceased within the scientific community. These may either lean toward protecting human health or toward protecting economic enterprise. In the former case a significant increase in benign tumors would be considered to be an index of carcinogenicity. In the latter case less weight would be placed on benign tumors." (Bates, S. 19–21)

c. OSHA's Conclusions

On reviewing the Record on this topic, OSHA makes two general conclusions based on substantial evidence in the Record:

1. Despite the range of opinions expressed on the issue, comparatively few well documented studies of the progression of tumors were presented in the Record. Where such studies were presented (e.g. those of Reuber (1977a, b) on liver tumors in mice and rats, of Stewart (Stewart, Tr. 634–635) on lung tumors in mice, or of Trump (Trump, S. 6–7) on kidney tumors in rats), they indicate that tumors often classified as "benign" are in fact merely stages in the progression to malignancy or are "malignant from the start".

2. No documented case was presented in the Record in which a substance was demonstrated to induce only benign tumors in animals.

Thus, OSHA concludes that the general principle enunciated in its proposed regulation, that a substance which induces benign tumors in an animal test should be regarded as a potential occupational carcinogen, was well supported by the *scientific* evidence presented at the hearing. OSHA notes that this proposition is accepted by EPA and used in its regulatory decisions (EPA, S. 3). OSHA recognizes, however, that some scientists disagree with the principle, even though they are unable to name specific chemicals which would justify consideration as exceptions. OSHA also notes that the NCAB Subcommittee and the IARC recommended that chemicals which induce only benign tumors should not be categorized unequivocally as carcinogenic.

For these reasons, OSHA is willing to consider evidence that a substance induces "only" benign tumors, provided that such evidence reaches the minimum scientific criteria for acceptability specified herein. For the reasons given in testimony of such witnesses as Dr. Stewart, Dr. Bates, Dr. Reuber, and Dr. Dubin, OSHA will not ordinarily consider arguments that liver or lung tumors in mice are benign for the purposes of this rebuttal.

In sum, the evidence presented in the Record and reviewed above indicates that essentially all known carcinogens* induce either malignant tumors, or a mixture of benign and malignant tumors, or benign tumors of a type which forms part of a progression to malignant tumors and thus have the capacity to progress to malignancy. Indeed, there was substantial testimony that the term "benign tumor" is in many cases inappropriate when applied to experimental carcinogenesis studies and is used in a misleading fashion. Accordingly, OSHA will not ordinarily place weight on the purported distinction between "benign" and malignant tumors in experimental animal studies. Since no documented case was presented in the Record in which a substance was demonstrated to induce only benign tumors, the issue is largely academic. However, OSHA notes that there was a body of scientific opinion that would place lesser weight on such hypothetical substances, if they should be found to exist. Accordingly, to avoid foreclosing an issue that may perhaps prove to have some genuine scientific content, OSHA is willing to consider good evidence that a substance has been shown to induce only benign tumors. However, to avoid wasting time and resources on repetition of the lengthy and often academic discussion of the issue presented in this Record, OSHA will require a reasonable showing that the evidence is substantial. Accordingly, OSHA has established modest criteria which such evidence must meet before it will be considered in rulemakings on specific substances. Specifically section 1990.143(i) states:

(i) *Benign tumors.* Results based on the induction of benign or malignant tumors, or both, will be used to establish a qualitative inference of carcinogenic hazard to workers. Arguments that substances that induce benign tumors do not present a carcinogenic risk to workers will be considered only if evidence that meets the criteria set forth in 1990.144(e) is provided.

Section 1990.144(e) provides:

(e) *Benign tumors.* The Secretary will consider evidence that the substance subject to the rulemaking proceeding is capable only of inducing benign tumors in human or experimental animals provided that the evidence for the specific substance meets the following criteria:

Criteria. (i) Data are available from at least two well-conducted bioassays in each of two species of mammals (or from equivalent evidence in more than two species).

(ii) Each of the bioassays to be considered has been conducted for the full lifetime of the experimental animals.

(iii) The relevant tissue slides are made available to OSHA or its designee and the diagnoses of the tumors as benign are made by at least one qualified pathologist who has personally examined each of the slides and who provides specific diagnostic criteria and descriptions; and

(iv) All of the induced tumors must be shown to belong to a type which is known not to progress to malignancy or to be at a benign stage when observed. In the latter case, data must be presented to show that multiple sections of the affected organ(s) were adequately examined to search for invasion of the tumor cells into adjacent tissue, and that multiple sections of other organs were adequately examined to search for tumor metastases.

The first criterion is related to the quantity of evidence. It is obviously insufficient to present evidence from only one species, since some chemicals are known to induce primarily benign tumors in one species and primarily malignant tumors in another. Moreover, in view of the testimony of Dr. Bates (S.

*In strict parlance, the term "carcinogen" should apply only to agents which induce carcinomas. The term is used here in its broad sense, to include agents which include sarcomas, leukemias, and "benign" epithelial tumors. Some regulatory scientists also use the term "oncogen" to encompass these agents.

21) on the role of genetics in determining the degree of malignancy of induced tumors, it would be desirable to have data from more than one strain of each species. Certainly a single experiment from each of two species would not provide substantial evidence that a chemical induces *only* benign tumors in each. For these reasons, although OSHA will not insist on the presentation of data from more than one strain of each species, OSHA will establish, as a minimum criterion, that data be available from at least two experiments in each of two species or from equivalent evidence in more than two species.

The second criterion is concerned with the duration of the experiments. Since many so-called "benign" tumors eventually progress to malignancy if the animal is allowed to live long enough, data from experiments which are terminated prior to the natural lifespan of the species involved are of little or no value for this purpose. Hence OSHA will require, as a minimum, that the experiments be conducted for the lifespans of the animals involved, and that a substantial number of animals should actually live to their expected lifespans. As a general guideline, minimum figures for expected lifespan would be 21 months for mice and 24 months for rats.

The third and fourth criteria are related to the identification of the induced tumors as benign. It is apparent from the testimony of eminent witnesses such as Dr. Stewart, Dr. Bates, Dr. Saffiotti and Dr. Dubin, that many tumors often reported by less knowledgeable pathologists as "benign" are in fact part of a progression to malignancy or are malignant from the start. Thus, for example, OSHA will not accept claims that liver-cell tumors or alveologenic lung tumors in mice are benign (see testimony of Dr. Reuber and Dr. Stewart quoted above). As a minimum criterion, as pointed out, OSHA will require that the diagnoses of induced tumors as benign should have been made by a qualified pathologist (preferably Board-certified) who has personally examined each of the tissue slides which are alleged to show benign tumors, and should be accompanied by specific diagnostic criteria and descriptions. In addition, documented reasons should be given for excluding the possiblility that the tumors are part of a malignant progression, or for concluding that all the tumors were at a benign stage when observed. In the latter case, data must be presented to show that multiple sections of likely target organs were made to search for evidence of invasion or metastases.

As discussed more fully above (Sections V.D.1 and V.D.6) there is often considerable disagreement among pathologists as to whether specific tumors should be classified as benign or malignant.* The reasons for these disagreements include the application of different criteria for malignancy (see statements of Dr. William H. Butler (NACA), Dr. Stan Vesselinovitch (NACA), and Dr. Harold Stewart (NIH)), inexperience and even bias among certain pathologists (for discussion see Stewart 1977, Exhibit C to Stewart statement, pp 310–311). Furthermore, some experiments reported in the past have suffered from substantial shortcomings, as pointed out from personal professional experience by Dr. Adrian Gross (FDA) (S.13–14). Accordingly, OSHA cannot automatically accept at face value any claim that an experimental study yielded tumors that were exclusively benign. At the minimum, OSHA will require that the relevant tissue slides should be made available. OSHA may, at the Secretary's discretion, submit the slides to a second pathologist selected by OSHA for an independent review. Even if both pathologists concur in their diagnoses, OSHA has concluded that it may be important in view of the scientific disagreements in this area that in any given case, each pathologist should provide specific criteria for their diagnostic categories, and that descriptions or illustrations should be provided to permit evaluation by other interested parties.

OSHA concludes, after review of the substantial evidence in the Record, that these criteria are reasonable, and that meeting them they will permit the consideration of any good evidence that a substance induces only benign tumors. At the same time, the minimum criteria will contribute to efficient regulation by discouraging frivolous or unscientific arguments.

*Some participants, such as the National Agricultural Chemicals Association (NACA) and its witness, Dr. William Butler, argued that in some cases, such as mouse liver tumors, this disagreement is irreconcilable, because there is insufficient scientific knowledge about their biological behavior. Although OSHA does not accept these arguments, if they were correct they would imply that benign tumors could not be reliably diagnosed, so that it would be academic even to consider giving them special treatment in regulatory classifications.

7. How Much Weight Should Be Placed on the Induction of a Type of Tumor Which Occurs Spontaneously in Untreated Animals?

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA discussed how much weight should be placed on experiments in which administration of a substance under test merely increases the frequency of a type of tumor which occurs spontaneously in the control (untreated) animals involved in the experiment. OSHA proposed to interpret the results of experiments showing an increased incidence of tumors in treated animals as positive evidence of carcinogenicity, regardless of the spontaneous tumor incidence in the controls, provided that the experiments were sufficiently well controlled and the increase in incidence of tumors was statistically significant.

b. The Public's Response and OSHA's Evaluation

Some witnesses and participants argued that substances which increase the frequency of a type of tumor which occurs spontaneously in the test animals should not be classified as carcinogenic *per se*, but be merely viewed as "augmenting" or "enhancing" agents, insofar as that study is concerned. However, such a view was not supported by the Record, including the expert scientific committees which have reviewed this problem as will be discussed below:

"For present practical purposes, no distinction is made between the induction of tumors and the enhancement of tumor incidence, although it is noted that there may be fundamental differences in mechanisms that will eventually be elucidated." (IARC, 1972, Vol. 1, p. 10)

and:

". . . it is not possible to differentiate clearly between initiating agents, promoting agents, and certain modifying factors. Any factor or combination of factors which increases the risk of cancer in humans is of concern regardless of its mechanism of action." (NCAB Report, 1977, p. 461)

A more substantial argument that was raised is that certain animal strains may be inappropriate for testing because of high and variable spontaneous incidence of tumors in one or more organs. This argument was made with particular reference to liver tumors in certain strains of mice, but was also made in reference to lymphosarcomas in mice, and certain other tumors. The NCAB Report cautioned against unequivocal reliance on:

"[b]ioassays employing inbred strains of animals which develop high incidences of particular tumors in the untreated state. In some of the studies the particular characteristics of the animals and the results obtained may require additional evaluation—in other instances, such well controlled test systems may be quite satisfactory for the establishment of carcinogenicity of an agent." (NCAB Report, 1977, p. 462)

Other expert committees, however, expressed no such reservations, merely emphasizing that the spontaneous incidence of tumors be carefully recorded (Mrak Commission, 1969, p. 465; UICC, 1969, p. 17), and in some cases recommending the use of genetically inbred strains with known spontaneous tumor incidence for specific bioassay purposes (UICC 1969, p. 16; NAS Principles for Evaluating Chemicals, 1975, p. 135; FDA Panel, 1971, p. 422). It was also pointed out that where the spontaneous incidence of tumors is high or even 100%, reliable inferences of carcinogenicity can be drawn from a decrease in the latency periods or an increase in the number of tumors per animal (IARC, 1972, Vol. 1, p. 10; FDA Panel, 1971, p. 420). In such cases, the emphasis that the study be "well controlled" (NCAB Report, 1977, p. 462) is important since the incidence of spontaneous tumors may depend on age or other factors, which therefore must be maintained the same in control and treated groups.

A number of witnesses addressed this issue and a range of opinions was expressed. Dr. Francis J. C. Roe (AIHC) wrote that the use of inbred strains of mice with high spontaneous tumor incidence is equivalent to using a "dirty test tube" (Roe and Tucker, 1973). He and Dr. Robert Olson (St. Louis Univ.) argued that the substances being tested may be acting as co-carcinogens and simply accelerating an inherent neoplastic tendency (Olson, S. 15). In addition, Dr. Olson discussed a number of non-specific stimuli known or believed to influence the frequency of spontaneous tumors in the mouse. He and others argued that this "hypersensitivity" to such stimuli as diet, stress, and viruses makes it difficult, if not impossible, to distinguish between these effects and those due to carcinogens.

Dr. James Jandl (Harvard Univ.) wrote that many of these high incidence strains are higly sensitive to the induction of spontaneous tumors and that the increased sensitivity is thought to be due to defects in DNA repair, detoxification, and metabolism. Dr. Jandl concluded:

"[i]t is highly unlikely that one can place credence upon the tests conducted in rodents, particularly inbred mice and inbred rats which are quite distant from man, which have different detoxifying and metabolizing properties, which have the unpleasant habit of copropagy, and which have so short a life span that doses employed in testing them are hundreds or thousands or tens of thousands greater than those to which occupational personnel would be exposed." (Jandl, S. 36–37)

Dr. Arthur Furst (Univ. of San Francisco) stated that certain strains of test animals with high spontaneous tumor incidence should not be used for specific test purposes:

"Another area for consideration is the natural history of the spontaneous tumors found in test animals. If the controls have a greater incidence of any spontaneous tumor than is expected from historical data, this experiment cannot be valid. Other criterion should include the specific strain of the species which should not be used for an experiment. For example, if mammary tumors are to be expected, the C3H mouse cannot be used; if pumonary tumors are to be investigated, strain A mice cannot be used; if testicular tumors are anticipated, then Fischer–344 rats cannot be used. This means that no single species or strain can become standard for all animal bioassays." (Furst, S. 22–23)

On the other hand, Drs. Robert Snyder and Anthony Triolo (American Iron and Steel Institute) expressed an opposite viewpoint:

"For a given strain of mouse, the susceptibility of a given target organ to the induction of tumors by chemicals seems to parallel the spontaneous frequency of tumors in that organ (Shimkin, 1940). When a tumor is described as being spontaneous, it means that the causes are unknown. For example, the A/J strain of mouse has a high incidence of spontaneous lung tumors (up to 78%) reaching its maximum at 20 months of age. In this strain of mouse, the latency is shortened and the incidence of tumors and the number of individual tumors per animal are increased following the administration of various tumorigenic alkylating agents (Shimkin, *et al.*, 1966). By contrast, the C57 black strain of mouse has a low spontaneous rate of lung tumor formation and tends to be resistant to the induction of lung tumors after exposure to chemical agents."

"Thus, if carcinogenic activity were being tested in the C57 strain after administration of a chemical capable of inducing lung tumors, the data would most likely suggest that the chemical was not carcinogenic. On the other hand, a similar test conducted in the A/J strain of mouse could very well show a carcinogenic effect for lung. Also, if the B6C3F1 mouse were used as a test animal, as suggested in "Guidelines for Carcinogen Bioassay in Small Animals" (Sontag *et al.*, 1976), tumors induced by chemicals in the mammary glands, spleen, pancreas, urinary bladder, ovary, uterus, adrenals and thyroid might go undetected due to the low spontaneous tumor incidence at these target organs in this particular strain of mouse (Page, 1977)." (Snyder and Triolo, S. 24–25)

Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska) took issue with NCAB's position, quoted above, that no practical distinction should be made between induction of tumors and the enhancement of tumor incidence:

"This categorical stand (apparently adopted for "policy" rather than scientific reasons) is again out of date. The NCAB subcommittee listed several pointers "to potential carcinogenicity—which require additional studies before they can be extrapolated to man." These include "Bioassays employing inbred strains of animals which develop high incidences of particular tumors in the untreated state." It would seem to be a matter of common sense to distinguish between an experiment in which a leukemia incidence of say 95% in the control animals was merely a change in the latent period and occurred a month early and another in which the experimental animals developed bladder cancers and the controls developed none." (Shubik, S. 19–20)

However, the NCAB Subcommittee did not make such a statement. The Subcommittee actually stated that such methods "*may* require additional studies before extrapolation to *particular conditions of human usage* can be made." The Subcommittee also stated that only *some* of these bioassays "may require additional evaluation—in other instances, such well controlled test conditions may be quite satisfactory for the establishment of carcinogenicity of an agent." (NCAB Report, 1977, p. 462)

Dr. William Butler (NACA) made the following statement:

"At the present moment, an animal with a high spontaneous incidence of a specific lesion, which may be modified by treatment by an exogeneous chemical, would be an inappropriate species. An increase of a neoplasm of already high incidence gives no confidence that the agent has induced a neoplasm. There is no validity in the suggestion that animals showing a very low or nil incidence of a neoplasm are not susceptible to induction of that neoplasm." (Butler, S. 15)

Other comments expressing the opinion that it is inappropriate to base conclusions upon increased incidence of tumors that occur spontaneously were made by Dr. H. G. S. Van Raalte (AIHC), S. 16, Dr. Frank C. Lu (Univ. of Miami), S. 6, and Dr. Johannes Clemmesen (Danish Cancer Registry), S. 8.

Many other scientists, however, have expressed the view that species with high spontaneous evidence of tumors are appropriate for bioassay purposes and this was the view of three expert committees. Only the NCAB Subcommittee expressed even partial reservations about the use of strains of animals with high incidences of spontaneous tumors.

A number of distinguished witnesses at the hearing expressed support for the position of the expert committees. Dr. Arthur Upton (Director, NCI) testified at length on this issue:

"Arguments are sometimes made that certain types of animal models, as certain methods of testing, have limited relevance to predicting the potential for human risk. Although these arguments are often scientifically trivial, they have sometimes generated considerable heat in cases where these methods of testing show the carcinogenicity of economically important chemicals. I would like to comment on two of these arguments, on which OSHA invited comment in its proposal."

"1. Objections are sometimes raised to the use of a mouse as a test animal, especially when a chemical gives rise to an increase only in liver tumors. One argument that is made to support such objections is that mice have an "unacceptably" high spontaneous incidence of liver tumors. There are several reasons why such an argument is untenable. Apart from the fact that the use of the mouse has been universally endorsed by expert committees and regulatory agencies, mouse liver tumors, in fact, appear to be a good model for at least certain types of human cancer. Several agents known to be carcinogenic in humans also induce tumors in the mouse liver, although in most cases they affect predominantly other organs in humans.

"More generally, the apparent susceptibility of mice to liver tumors should not make the mouse inappropriate for use in testing. It is elemental in carcinogenicity testing that not all mammalian test species—be they mice, rats, hamsters, others—show the same incidence of spontaneous tumors. Some strains and species are more susceptible than others, and picking an appropriate test strain is a fundamental consideration in planning a carcinogenicity test. In general, the strain chosen should have a good susceptibility to carcinogens, and one reason that the mouse is a good test animal is that we have more knowledge of the mouse and more inbred strains of the mouse to work with than is the case with other test species. I find it somewhat misleading, therefore, to speak of a test *species* as exhibiting particular characteristics, since through genetic breeding we have established diverse strains within species, each differing in its characteristics from others.

"2. A related argument is that less weight should be placed on results obtained in strains of animals in which there is a high spontaneous incidence of the type of tumor induced by the compound. The argument may be paraphrased as follows: Even if an increased incidence of tumors is found in test animals after exposure to a particular compound, one cannot properly infer the test agent "caused" the induction of such tumors; one can state only that a statistical association was demonstrated between administration of the compound and the elevated incidence of tumors; one must know the mechanisms by which a carcinogenic response is elicited before one can speak to the question of "causation" or label a test compound a "carcinogen".

"I do not subscribe to this position. In carcinogenicity testing today we base findings of carcinogenicity on precisely recorded experimental comparisons of treated and untreated groups of animals, and I believe it not only proper but important that we do so. Given our present state of knowledge concerning the mechanisms of carcinogenicity, it may be some time before we can reliably establish the entire pathway from administration of a carcinogenic agent to the appearance of a carcinogenic response. To require that such a pathway be established in detail before an agent can be labelled "carcinogenic" would be to adopt the ostrich-like position of ignoring facts which constitute obvious warning flags for human health."

* * * * *

"Because of incomplete knowledge concerning mechanisms, I also do not believe that distinctions between "carcinogens" and "co-carcinogens", or between "causative agents" and "enhancing agents" can be considered relevant today when ascertaining hazards to human health arising from carcinogens. In safety testing of carcinogens today, we are concerned with one question: "Does exposure to the test agent result in a significant induction of tumors in exposed populations as compared to controls?" If so, then the test agent has elicited a carcinogenic response and must, therefore, be considered potentially hazardous to human health. Precise knowledge of the mechanism of action of the carcinogen or possible co-factors in the host animal is not required for preventive action unless and until we know that similar co-factors are not also found in man. Until we have such knowledge, it is difficult to make practical distinctions between "carcinogens" and "co-carcinogens" and between "causative agents" versus "enhancing agents." (Upton, S. 13–17)

Dr. Robert Squire (Johns Hopkins Univ.) explained:

"Tumors that normally occur with a high or variable incidence are more likely than others to be misinterpreted, because of statistical type I errors, as positive results of the exposure (Fears, 1977; Hoel, 1977). Examples include liver, lung, and hematopoietic neoplasms in certain strains of mice. Even at these sites, however, carcinogenic effects may be clearly demonstrated by obvious increases in tumor incidences or decreases in latency periods." (Squire, S. 12)

Dr. Bernard Weinstein, (Columbia Univ.) agreed that a well controlled study is able to predict a carcinogenic risk for man. A high level of spontaneous tumors only results in a loss of sensitivity for detecting a carcinogenic effect.

Dr. Walter Heston (NCI) stated:

"[w]hile it is true that such enhancement may come about by mechanisms many which are not relevant to humans, it is also [true] that the same [or] related mechanisms may indeed operate in humans. Moreover, it is not known whether human tumors which do appear are "spontaneous," chemically-induced, or the result of chemical enhancement of a neospontaneous state in otherwise normal cells. Thus, I feel that a reproducible chemical enhancement of spontaneously occurring tumors can be considered as evidence that the chemical is hazardous to man—the chemical may indeed be carcinogenic in man." (Heston, Post-hearing Comment, p. 24)

As pointed out by Dr. Heston, many of the non-specific stimuli mentioned by Dr. Olsen have been implicated in human carcinogenesis. The role of diet in human cancer was discussed by Armstrong (1977) who listed four possible mechanisms by which diet can influence human carcinogenesis:

"Recent interest in the role of diet in human carcinogenesis has arisen from experimental studies of diet and cancer in animals (reviewed by Clayson 1975), descriptive epidemiologic studies showing correlations between national cancer rates and consumption of foodstuffs (reviewed by Armstrong and Doll 1975), studies of changes in cancer incidence and dietary habits with migration (Haenszel and Kurihara 1968), and analytic studies relating cancer risk to the dietary habits of individuals (for example, case-control studies in the Hawaiian Japanese; Haenszel et al. 1973).

"The following is suggested as a classification of possible mechanisms for the role of diet in human carcinogenesis:

1. Ingestion of carcinogens or carcinogen precursors.

2. Effects on the production, activation, or inactivation of carcinogens by the intestinal flora.

3. Effects on the endogenous production, activation, or inactivation of carcinogens.

4. Effects on tissues to alter their susceptibility to carcinogenesis.

"Epidemiologic data are available which illustrate with varying degrees of certainty each of these possible mechanisms." (Armstrong, 1977, p. 557)

However, we are far from being able to predict when and under what circumstances these interactions will occur in humans. The situation is no different with experimental animals.

Dr. John Berg (Colorado Regional Cancer Center) also made this point when discussing the complexity of human carcinogenesis:

"Bowel cancer undoubtedly is related in some way to diet. We don't yet know the carcinogen involved, though several candidates are under investigation. We do know, however, that bile acids are good *promoters* of colon carcinogenesis, that fat in the diet increases the output of bile acids and that bowel cancer around the world is highly correlated with fat intake. We also know that bowel cancer risk, other things being equal, is lowered in people who eat more fruits and vegetables. We also know the vitamin C and naturally occuring food constituents act as antioxidants to reduce the activity of carcinogens, so we have identified some tertiary factors affecting bowel cancers (the promoters are secondary factors). Finally we

have reason to believe that, given the same intake of carcinogens, the same level of promoters and of antioxidants, increasing dietary fiber may slightly lower cancer risk. We don't know yet which factors will be easiest to change or which changes will have the biggest influence on risk but we do know that the combination is far more deadly than any single substance." (Berg, S. 16)

Dr. Berg also noted that correlations of this sort also exist for cancer of the stomach, esophagus, and prostate.

The thesis presented by Dr. Olson and others, that mice of high incidence strains are uniquely susceptible to these influences is therefore unacceptable. Many witnesses agreed that certain strains or species of animals are genetically predisposed to cancer. What was not so readily recognized is that similar situations exist for human cancers. Epidemiological studies of cancer incidence in human populations indicate a relationship between genetic susceptibility and the appearance of various types of cancers. Dr. Robert Squire (Johns Hopkins Univ.) listed several examples of this interaction:

"Examples include leukemia, Wilm's tumor, retinoblastoma, and skin cancer. Evidence of familial predisposition to breast cancer, certain endocrine gland tumors, and colon cancer also exists (Mulvihill 1975; Kellerman 1977). These genetically predisposed cancers represent only a small proportion (1–2%) of the total human cancer burden (Knudson 1977). However, there is also reason to be concerned about interaction between environmental factors and genetic predisposition in segments of the population. An example is the association between genetically determined aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma (Kellerman 1977)." (Squire, S. 4)

Dr. David Kaufman (Univ. of N. Carolina) also referred to genetic effects on "spontaneous" tumor incidence in man:

"An individual's genetic inheritance also appears to have a significant role in determining risk to malignancy. It is clear that individuals with genetically acquired diseases such as xeroderma pigmentosa, ataxia telangiectasia, Fanconi's anemia, and familial polyposis of the colon, to name but a few, are at increased risk to various neoplasms (37). Since individuals who are homozygous and manifest the symptoms of the first three diseases cited are rare and generally die young, they are unlikely to be members of the work force. The pool of individuals who are heterozygous and carry the recessive gene responsible for Fanconi's anemia and ataxia telangiectasia are not rare. It has been estimated that approximately 1% and 0.3% of populations within the United States are heterozygous carriers of the genes of ataxia telangiectasia (38) and Fanconi's anemia (39). Epidemiologic studies have shown that individuals who carry these recessive genes are at an increased risk for the development of malignant tumors (38, 39). Unfortunately, individuals carrying these recessive traits are now only detectable by their familial relationship to a homozygous individual suffering from these diseases. Thus, no predictive test is available for their identification. The cited examples are but a few of the more numerous genetically determined diseases which have been associated with an increased risk of malignancy. It is not difficult to imagine that these are manifestations of only the more obvious genetic variations in the human population. It is plausible that the variability in familial risks of malignant disease is, to some degree, related to a variety of genetic properties as yet unidentified." (Kaufman, S. 16–17)

Dr. Walter Heston (NCI) also pointed out that susceptible genotypes exist in the human population. It has been shown that lung cancer is aggregated in families independently of smoking habits. He stated:

"[t]his is evidence that genetic predisposition to cancer, much like what we have observed in inbred strains of mice, may be critical in the chemical induction of cancer in humans." (Heston, Post-hearing Comment, p. 25)

Therefore a large amount of evidence supports the idea that cancer in both humans and animals may arise due to the exposure of susceptible individuals to carcinogens. The fact that a particular strain of mice has a high spontaneous tumor incidence should not disqualify it from being used to identify carcinogens. Induction of tumors in such an animal is no less relevant for the purpose of identifying carcinogens than the use of a low resistance strain. This was illustrated by a study described by Dr. Heston:

"Lynch (1943) studied the relationship of spontaneous lung cancer and induced lung cancer in three mouse strains. The three strains were selected because they represent strains with high, medium, and low spontaneous tumors of the lung. Strains and their spontaneous lung tumor rates were: Swiss inbreds (predecessor of the SWR strain): 46.1%; Bagg (inbred predecessors of the BALB/c strain): 26.3%; and strain 1194, 4.6%. These strains included mice of all ages. Mice were injected intraperitoneally with 0.125 mg of a 0.4% solution of 1,2,5,6 dibenzanthracene in olive oil at 2 to 4 days of age. Induction of lung tumors was found to be related to the susceptibility of each strain to spontaneous tumors. Thus, in Swiss mice, 100% of the mice showed from 24 to 86 lung tumors/mouse 65 to 75 days after injection. The Bagg mice showed 100% incidence with 27 to 61 tumors per mouse 210 days after injection, and strain 1194 mice showed a 50% incidence, with no mouse having over 5 tumors, 175 to 210 days after injection. Thus the carcinogenic effects of dibenzanthracene were seen in all three strains, but the Swiss mice were the most sensitive indicators of carcinogenic activity." (Heston, Post-hearing Comment, pp. 25–26)

Two additional points were made in testimony and exhibits at the hearing. First, as suggested by Dr. Heston above, recent studies of the mechanisms of cancer induction suggested that animals with relatively high spontaneous tumor incidence may in fact be *more* appropriate for assaying potential carcinogens than animals with low or zero spontaneous incidence:

"One practical implication of the fact that different carcinogens share many mechanistic steps is that enhancement of certain carcinogenic processes may have a more readily detectable effect on cancer incidence in animals with high background levels of all other carcinogenic processes. Therefore carcinogenicity tests of various substances should possibly include tests on high spontaneous incidence strains or experiments to see whether the test substance enhances the carcinogenic effect of a standard carcinogen." (Crump *et al.*, 1976, p. 2977; Annex C(a) to Peto Statement)

Second, for statistical reasons, the use of animals with high spontaneous incidence is likely to lead to false negative results rather than false positives:

"Any animal that has a high incidence of "spontaneous" tumors should be regarded as unsatisfactory. Not only is a positive result more difficult to establish in statistical terms unless large numbers of animals are used, but a positive result may fail to be elicited, thereby producing a false negative result. This is the most serious error of any system for detecting carcinogenic activity. (Crampton, S. 6)

* * * * *

"Spontaneous tumors occur at different sites in virtually every species and strains thus far tested. The organs affected and numbers of tumors vary. The inbred strains developed by researchers have been either to increase sensitivity or to avoid certain inherent weaknesses such as spontaneous tumors and diseases not related to the chemical. From a purely statistical standpoint, animal studies that have a low spontaneous incidence of cancer in a target organ of concern are preferred." (PPG, S. 26)

c. OSHA's Conclusions

Based on review of the evidence in the Record, OSHA finds no scientific reason to modify its original proposal on this issue. OSHA believes that because it was not as clear as it might have been that OSHA intended that results in animal testing were to be statistically reviewed for significance in all cases, many participants may have replied to this issue and perhaps over-emphasized the issue concerning the use of animals with high rates of spontaneous tumors. In any event, although some scientists may prefer results obtained in strains of animals with low spontaneous tumor incidence, for statistical and other reasons, OSHA believes that results

obtained in high incidence strains are valid indicators of carcinogenicity, provided that the experiments are well controlled and the observed increases in tumor incidence are statistically significant. OSHA will consider evidence that the tumor incidence and rate of development are related to random variation within a control range when good data are available for control animals of the strain under consideration from the laboratory reporting the test results. Indeed, because a species of animal has a very low or zero spontaneous incidence of tumors at various sites, this may indicate that it is resistant to the induction of tumors at these sites by carcinogens, and hence would be unsuitable as an experimental subject and for this reason, the use of positive controls in carcinogenesis bioassays has been recommended by some expert committees (Mrak Commission, 1969, p. 467). As in other aspects of evaluation of experiments, interpretation of such data requires the exercise of good scientific judgment which includes the determination and review of statistical and biological significance. Thus, OSHA's Cancer Policy specifically provides in section 1990.143(e):

"(e) *Spontaneous tumors.* Positive results in human or mammalian studies for the induction or acceleration of induction of tumors of a type which occurs "spontaneously" in unexposed individuals, will be used for the qualitative identification of potential occupational carcinogens."

8. Routes of Administration

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA specifically requested the public participants to the rulemaking to address the question:

"Which routes of exposure of experimental animals are to be considered appropriate for extrapolation to man?"

Specific attention was drawn to this question because occupational exposure to carcinogens may often be either by way of dermal or inhalation exposure, whereas studies with experimental animals often involve other types of exposure or administration, such as oral exposure, or in some cases exposure by skin painting or injection. In the proposed regulation, OSHA proposed to utilize positive results for carcinogenic activity obtained from most routes of exposure, with the specific exception of carcinogenesis resulting from injections or implantations, in which the tumors are induced only at the site of application. OSHA stated that it intended to consider each case on its merits, subject to the following guiding principles:

"(1) Oncogenic effects resulting from dermal, inhalation, injection (with tumors at distant sites) and oral exposure (including gavage or intratracheal instillation), shall be regarded as directly relevant to occupational exposure, except in special circumstances;

(2) Carcinogenesis resulting from injections or implantations, in which the tumors are induced only at the site of application, shall generally be regarded as irrelevant to occupational exposure, except where the substance is distributed systemically or in other special circumstances." (42 FR 54164)

b. The Public's Response and OSHA's Evaluation

The general issue raised was whether a positive result obtained in an experiment with animals exposed by one route of administration justifies an inference of carcinogenic hazard to humans who might be primarily exposed by another route of exposure. If so, the next question becomes whether all routes of exposure provide equally valid evidence for drawing inferences of carcinogenicity, or whether some routes of exposure are to be regarded as inappropriate? The specific issues as addressed in the proceeding were the following:

1. Is the general proposition correct, that a positive result obtained in an experiment with animals exposed by one route justifies an inference of carcinogenic risk to humans exposed by another route, or, in the alternative, should OSHA utilize data only from experiments in animals exposed by the same route as that of occupational exposure?

2. Should weight be placed on the induction of tumors at the site of injection or implantation, and if so, in what circumstances?

3. Are there routes of exposure that can be categorized as just inappropriate in the determination that a substance poses a potential occupational hazard to humans?

(1) Are most routes of administration appropriate?

Most witnesses expressed support for the proposal as it related to the qualitative identification of a carcinogenic hazard. A number of witnesses expressed support for the general proposition that positive results obtained by various routes of exposure can be used as the basis for determination of carcinogenicity and for extrapolation to infer risk to humans or animals exposed by other routes.

For example, Dr. Richard Griesemer (NCI) stated that:

"There is no unique route of exposure for animals that must be employed for the results to be relevant to predicting human risks." (Griesemer, S.8)

He further stated:

"When the objective of the experiment is to determine the capability of the chemical to produce cancer, the appropriate route of exposure is the one in which it is demonstrated that the chemical has reached all the parts of the body." (Griesemer, S. 8)

Dr. Benjamin Van Duuren (NYU) cited four examples from his own work which indicate that a substance found carcinogenic by one route characteristically is carcinogenic when tested by another route. The examples were chloromethylmethyl ether (CMME), bis-chloromethyl ether (BCME), epichlorohydrin, and dimethyl carbamoyl chloride (DMCC):

"Each of these compounds was first shown to cause squamous carcinoma when applied to the skin of mice and sarcomas in mice exposed by intraperitoneal and subcutaneous injection. In subsequent inhalation exposure studies, CMME and BCME caused squamous carcinoma of the bronchial epithelium in rats; epichlorohydrin and DMCC caused squamous carcinoma of the nasal epithelium. CMME and BCME are now accepted as human carcinogens (lung cancer) because of the results of epidemiologic studies" (Van Duuren, S.6, references omitted)

Dr. Van Duuren (NYU) during his oral testimony reaffirmed this position:

"It is desirable but not always that important. And I can cite you several examples of this. Epichlorohydrin is a very widely used industrial chemical. We show that it does not cause skin tumors in mice; it did cause sarcomas by subcutaneous injection in our own laboratory, and was subsequently shown in our Institute by inhalation to cause nasal epithelium carcinomas in rats by inhalation exposure. And therefore, the route of exposure, while it is desirable to have it the same as what the industrial exposure is, is not necessarily the critical factor." (Van Duuren, Tr. 1813)

Dr. Bo Holmberg (Swedish NBOSH), after considerable discussion of data regarding similarity of results among different routes of exposure for animal models anddhuman exposures, commented:

"No route of administration is *a priori* irrelevant to occupational exposure . . . as soon as a target dose high enough to produce cancer in a limited number of animals is obtained by one route of administration or another, the substance should be regarded as posing a cancer risk." (Holmberg, S. 24–25)

Dr. Lorenzo Tomatis (IARC) commented:

"The use of the same or similar routes of administration can result, although not consistantly, in tumors occurring at the same target organs in different species. The available evidence of human carcinogens indicates, however, that chemicals found carcinogenic to man were carcinogenic to animals when given by a variety of routes, most of them different from that by which humans are exposed." (Tomatis, S. 5)

In fact, Dr. Tomatis presented a table in one of his references (Tomatis, *et al.*, 1978, Appendix 5 to Tomatis Statement) which shows that 18/26 or 69% of the known human carcinogens have been tested by subcutaneous injection, intramuscular injection or intraperitoneal injections with positive results. His table, partially presented below, compares target organs and routes of exposure in animals and humans.

"Compound	Animal species	Route of exposure In animals/in humans
Aflatoxins	Mouse, Rat	i.p., s.c.-oral/inhalation.
4-aminobiphenyl	Mouse, Rat	s.c.-oral/inhalation.
Asbestos	Rat only	i.p., s.c.-oral/inhalation.
Auramine	Rat only	s.c.-oral/inhalation.
Benzidine	Mouse, Rat	s.c.-oral/inhalation.
Bis(chloromethyl) ether	Rat only	s.c.-inhalation.
Cadmium	Rat only	s.c., i.m.-oral/inhalation.
Chloromethylmethyl ether	Rat only	s.c.-inhalation.
Chromium	Mouse, Rat	s.c., i.m.-oral/inhalation.
Cyclophosphamide	Mouse, Rat	s.c., i.m.-inhalation.
Diethylstibestrol	Mouse, Rat, Hamster, Squirrel, Monkey.	s.c. (impla.), s.c. oral.
Hematite	Rat only	s.c.-inhalation.
Melphalan	Mouse, Rat	s.c.-oral, injection.
Mustard Gas	Mouse only	s.c.-inhalation.
2-Naphthylamine	Mouse only	s.c.-oral inhalation.
Nickel (implantation)	Mouse, Rat, Hamster	s.c., i.m.-inhalation (impla.).
N,N-Bis (2-chloroethyl) 2-naphthylamine	Rat only	s.c. oral.
Phenytoin	Mouse only	i.p.-oral injection.

NOTES

(I.p. = Intraperitoneal injection.
S.c. = Subcutaneous injection (unless otherwise noted).
I.m. = Intramuscular injection (unless otherwise noted)".
(Tomatis, *et al.* Appendix 5 to Tomatis Statement, pp. 879–880.)

Many witnesses agreed that experimental animal bioassays conducted by inhalation, dermal, or oral routes of exposure, while the likely human exposure is by a different route, are appropriate for qualitatively identifying the carcinogenicity potential to humans. These witnesses included Dr. Arther Upton (Director, NCI), Tr. 324–325, Dr. David Rall (Director, NIEHS), Tr. 485, Dr. Donald Kennedy (Commissioner, FDA), Tr. 579–580, Dr. Renate Kimbrough (CDC), Tr. 1788, and Mr. Richard Peto (Oxford Univ.), Tr. 2521.

On the other hand, several witnesses expressed the opinion that experiments in animals should be conducted by the same routes of exposure as those by which humans are exposed. These witnesses included Dr. Carroll Weil (Carnegie-Mellon Univ.), S. 2–3; Dr. George Claus (AIHC), S. 12–13; Dr. Roy Albert (EPA), Tr. 2390; Dr. Francis J. C. Roe (AIHC), S. 76; and Ethyl Corporation, S. 17–19. However, it is not clear from the context of these comments that any of the witnesses was referring to the situation of direct concern to OSHA, *viz.* the qualitative interpretation of positive results in an animal experiment already conducted. For example, Dr. Carroll Weil of Carnegie-Mellon Institute of Research commented:

"Effects obtained by one route of administration to test animals are not a priori applicable to effects by another route of administration to man. The routes chosen for administration to test animals (in experiments to predict the degree of safety of a material for man) should, therefore, be the same as those to which man will be exposed. (Weil, S. 2–3)

This statement explicitly refers to experiments conducted "to predict the degree of safety of a material for man", and not to the use of a positive result to infer hazards. OSHA agrees that it may be appropriate to require testing by the same routes as those by which humans are exposed if the purpose of the testing is to establish the *safety* of a material. This viewpoint was expressed by the Surgeon General's "expert" Ad Hoc Committee in 1970:

"No chemical substance should be assumed *safe* for human consumption without proper *negative* lifetime biological assays of adequate size. The minimum requirements for carcinogenesis bioassays should provide for: adequate numbers of animals of at least two species and both sexes with adequate controls, subjected for their lifetime to the administration of a suitable dose range, including the highest tolerated dose of the test material by routes of administration that include those by which man is exposed. Adequate documentation of the test conditions and pathologic standards employed are essential." (NCI Ad Hoc Committee 1970, p. 1, emphasis added; Exhibit 10(b) to Epstein Statement)

However, it would not follow that a positive result by any route should be deemed irrelevant.

Dr. George Claus (AIHC) cited certain substances which have been reported to be positive by one route in animal testing but negative when tested by another route (S. 12–13). Dr. William Lijinsky (NCI–FCRC) similarly cited polynuclear hydrocarbons as being negative by oral administration in mice while positive by skin application (S. 20).

However, such findings would not support an inference that the positive results were irrelevant to prediction of human risk. Rather, they would indicate that false negative results can be obtained with certain routes of exposure, so that testing by multiple routes would be necessary to provide reasonable assurance of safety (as indicated by the Ad Hoc Committee in the recommendation cited above.)

If it were practicable, it would be desirable to test chemicals by the routes of exposure most similar to those by which humans are exposed; by this means the most direct comparisons would be facilitated, at least so far as quantification of risk is concerned, discussed below. Several witnesses supported this general position during the hearings: Dr. Van Duuren (NYU) S. 5; Dr. Albert (EPA) Tr. 2386, 2390, NIOSH, Appendix *C*, p. 14, 15; Dr. Furst, S. 7; Dr. Weil (Carnegie-Mellon) S. 2–3; Stauffer Chemical Co., S. 3; Dr. Roe, S. 76. However, in occupational situations, workers are frequently exposed by multiple routes, usually by both dermal and inhalation routes and sometimes also by ingestion.

Dr. Bo Holmberg (Swedish NBOSH) commented further:

"Another reason for taking subcutaneous injections and similar routes of administration seriously is that many substances may penetrate the intact skin during occupational handling in amounts sufficient to induce cancer. The penetration of chemical substances additionally may be greatly enhanced by skin injuries or skin diseases, conditions which are common in

industrial work. Experimental studies where carcinogens are administered by subcutaneous or intramuscular injections are very close models to that practical situation." (Holmberg, S. 23)

Dr. Griesemer (NCI) commented:

"It should be noted, though, that for most chemicals man is exposed by multiple routes, most commonly by inhalation and dermal exposure in the workplace and by ingestion in the home. It may be noted, too, that the majority of inhaled particulates cleared from the lung are subsequently swallowed and that volatile chemicals (e.g. kerosene) may reach the respiratory tract after they are swallowed." (Griesemer, S. 7–8)

It would be very difficult in practice to design a bioassay in which animals were exposed by the combination of routes that would exactly match the human exposure. In any case, the issue facing OSHA is not the design of the most appropriate bioassay, but the interpretation of reported results of bioassays conducted in the past. Comparatively few substances have been tested for carcinogenicity by the inhalation route and it would not adequately protect employees for OSHA to limit its regulatory activity to these substances because evidence strongly indicates that other routes of exposure in animals accurately predict human response to carcinogens. This point was addressed in 1970 by the Surgeon General's Ad Hoc Committee:

"The present state of the art requires long-term biossays in mammalian species for the experimental identification of carcinogenic activity. United States law requires that food additives and various other materials be tested in animals by the intended route of human exposure. Similar tests have not been required for some materials to which humans are exposed by other than the oral route. The expanding production and use of chemicals in household products results in extensive human exposure (via the skin and respiratory tract) to dusts and aerosols; little information is available on the chronic toxicity of these materials by these routes of administration. It would not be wise to wait for the results of these "experiments in man" before instituting animal experimentation." (NCI Ad Hoc Committee, 1970 p. 6, Exhibit 10(b) to Epstein Statement.)

In any case serious scientific questions were raised during the rulemaking as to whether inhalation experiments on animals in fact constitute the most appropriate model for predicting carcinogenic risks to humans exposed by inhalation. Dr. Holmberg commented:

"The inhalation route of exposure in animal experimentation is generally considered most relevant to the occupational routes of entry of chemicals. It is, however, to be observed that inhalation studies in small rodents with polycylic hydrocarbons (PAH) generally have given negative results (Laskin and Sellakumar, 1974), although benzo (a) pyrene and other PAH's in tobacco smoke and in general air pollution are accepted as representing a human lung cancer risk. The results in the experimental studies are negative because the anatomy and the physiology of the rodent respiratory system do not allow the PAH to build up a lung tissue dose large enough for a sufficiently long time to permit the development of tumors in a limited number of animals. By intratracheal instillation or intrapulmonary implantation of the carcinogenic PAH's however, lung tumors are easily induced in experimental animals. If one completely discards experimental data obtained by subcutaneous injection, intramuscular, intravesicular or intrapulmonary implantation and similar routes of administration one is ignoring the fact that it is the target dose of the carcinogen which matters in cancer formation." (Holmberg, S. 24.)

Dr. David Kaufman (Univ. of N. Carolina) presented in detail the results of his own experiments involving intratracheal instillation of benzo(a)pyrene and/or ferric oxide in rodents (Kaufman, S. 10–12). His results provide detailed illustration of Dr. Holmberg's point that intratracheal instillation is an appropriate model for inhalation exposure of humans, because it permits the achievement of an adequate dose to the target issue.

Dr. William Lijinsky (Director, NCI–FCRC) also commented on one of the major drawbacks of inhalation as a route of exposure for animal testing:

"In the case of inhalation, it is impossible to achieve the goal of the standard test for carcinogenicity of applying the maximum tolerated dose. The maximum tolerated dose by inhalation is likely to be much lower than the maximally tolerated dose by feeding because inhalation involves a pathway of exposure. As a gas —, if the compound is a gas, which means that the density of the compound, the concentration of the compound, is low, it also involves the factor of toxicity by the inhalation route due to the particular biological nature of the compound. There are many compounds that are toxic by inhalation and much less toxic by feeding. Inhalation involves passage into the lungs. The substance might have a local effect on the lungs or the nasal passageways which would restrict the concentration you could apply to the animal. And I think that as a test method, inhalation is poor in testing for safety because of this restriction." (Lijinsky, Tr. 1081–1082.)

Dr. Griesemer similarly commented:

"Some routes of administration are less effective in animals because the dose that can be administered is limited, but this is not necessarily so in man. Therefore, in our animal tests, we usually administer the chemical by feeding because in that way we can apply a satisfactory dose." (Griesemer, Tr. 1020)

Dr. Samual Epstein (Univ. of Ill.) also commented on this issue:

"I would not be happy to develop negative inferences from carcinogenicity tests based on skin painting, because it is difficult to get an accurate dose into an animal by skin painting. I think that ideally one would like to see a mixture of two types of tests, feeding as a standard method of administration of substantive quantities of agents to an animal, and also inhalation. I think the inhalation experiments would be useful in certain defined circumstances, but I think the feeding is an adequate method of getting a range of doses into an animal, extending up to a maximally tolerated dose." (Epstein, Tr. 1367)

NIOSH explained other problems of inhalation testing:

"First of all, there is no equivalent to the olfactory pathway in man. Secondly, animals do not breathe through their mouth, which man does, so there are obvious differences between man and animals. * * * Also, obviously the particle size is important. Man may be able to take in larger particles than animals and it may reach different levels of the respiratory tree in man as opposed to animals." (NIOSH, Tr. 2949–50)

Thus, because of these inherent differences in the respiratory system between humans and animals, NIOSH agreed that if an experiment were limited to the inhalation route alone, the possibility of producing a false negative result would be increased.

2. Subcutaneous and Implantation Testing

There was considerable discussion in the Record of the appropriateness of experiments involving subcutaneous injections and implantations in evaluating human risk, and a wide range of opinions was expressed. In general, there were few substantial objections to the use of injections or implantations as a route of administration, provided that the material is distributed systemically and gives rise to tumors at sites distant from the point of injection. For example, the tabulation by Tomatis referred to above (Tomatis, *et al.* 1978, pp. 879–880; Appendix 5 to Tomatis Statement) shows that a number of substances known to be carcinogenic in humans have been shown to be carcinogenic in certain animal species, primarily by the

injection route. Dr. Arthur Furst (Univ. of San Francisco), in presenting a review of carcinogenic effects of metals (Furst and Haro, 1969; Appendix 1 to Furst Statement), stated as one of his proposed criteria for identification of carcinogens:

"The tumor induced should appear at a site distant from the site of application of the metal." (Furst, S. 2)

A paper by Dr. Michael B. Shimkin (Shimkin and Stoner, 1975: API Post-hearing Comment) which was introduced into the Record presented a review of a carcinogenesis bioassay technique involving the exposure of young strain A mice to chemicals by intravenous injections, with the subsequent observation of lung adenomas. The conclusion of his paper was:

"The lung tumor response in strain A mice is easily and clearly positive to all major types of chemical carcinogens. Estrogenic and other steroid hormones, with the targets of endocrine-regulated tissues, are an exception.

"The lung tumor of the mouse has demonstrated its ability to pick up undetected, unpredicted neoplastic responses, such as to urethane and to isoniazid. The carcinogens picked up by the lung tumor system, without exceptions known to us, have been shown to be carcinogenic for other tissues and in other species of animals. Although lung tumors are the earliest neoplasms induced by urethane, for example, further work showed the compound to be an intriguing multipotential carcinogen." (Shimkin and Stoner, 1975, p. 46–47; Hearing Exhibit 219)

The point at issue is, thus, not the appropriateness of exposure by injection, but the significance to be attached to the induction of tumors *only* at the site of injection or implantation. Some comments asserted that little or no weight should be placed on injection or implantation site tumors. For example, Standard Oil commented:

"Implantation site tumors may be first stage warnings of possible hazard and indicate the need for further testing; but unless tumors can be produced by inhalation, dermal, or oral routes, it is wrong to regulate the substance as a carcinogen." (Standard Oil, S. 13)

The NCAB Subcommittee report stated that:

"The criteria for extrapolation may vary depending on the agent in question. For example, demonstration that a compound only produces subcutaneous sarcomas in rodents may be relevant to a drug that will be injected subcutaneously in humans, but such animal data may not necessarily be appropriate in assessing the risks associated with a substance that humans will only receive orally. Because of the limitation inherent in animal bioassays, a negative result obtained in a particular animal bioassy does not exclude the potential carcinogenicity of a compound in humans. The inappropriate experimental species may have been chosen; the number of animals tested may have been too small; or the duration of observation may have been too short. Alternatively, test conditions may have been inappropriate in terms of their predictive value for the response of humans. The extrapolation of experimental carcinogenicity data to the human situation is strengthened by obtaining results in more than one species. Negative results obtained in one species do not, however, detract from the significance of clearly positive results obtained in another species." (NCAB Report, 1977, p. 463; Exhibit B to Weinstein Statement)

Dr. Samuel Epstein (Univ. of Ill.) stated in response to a question:

"Well, I would say that certain kinds of tests are not necessarily appropriate for occupational carcinogens, and I would not be willing to make formal extrapolations under most circumstances upon carcinogenicity data based on subcutaneous administration." (Epstein, Tr. 1367.)

However, other witnesses commented on the significance which should be attached to local tumor induction. In fact several witnesses provided detailed comment and discussion of this problem. Dr. Francis J. C. Roe (AIHC) commented:

"The statement that 'Tumors induced only at the site of application are generally irrelevant to occupational exposure unless the substance is distributed systemically' is manifestly wrong. The production of skin cancer by inadequately refined mineral oils does not depend on their systemic distribution, nor almost certainly does the production of lung cancer in response to the inhalation of bischloromethyl methyl ether." (Roe, S. 91.)

Two witnesses, Dr. Bo Holmberg (Swedish NBOSH) and Dr. Lorenzo Tomatis (IARC) provided detailed discussion of this problem. Dr. Holmberg commented:

"I would in this connection like to point out the many experiments performed with metals in rodents, where local tumors have been induced. Thus, intraosseal implantation of chromium, subcutaneous and intramuscular injections or intramuscular implantation of chromium metal and some chromium compounds have induced local sarcomas in rodents (IARC Vol. 2, 1973). Exposure to chromium compounds, particularly hexavalent compounds does represent a risk for lung cancer and possibly also for nasal cancer among smelting workers. Data on the mutagenicity of some chromium compounds also suggest a potential carcinogenic activity. The experimental data with chromium compounds obtained by subcutaneous and intramuscular implantation are therefore to be regarded as being relevant to occupational exposure, i.e., they are truly predictive of a risk of cancer at least in the organ of contact. Studies with some nickel compounds by subcutaneous injection in rodents (IARC Vol. 2, 1973 and Vol. 11, 1976) have also led to the induction of local tumors. Also in this case occupational exposure to nickel compounds in the metal refinery industry poses an increased risk for cancer in the organs of contact, the lungs, and the nasal cavity.

"Subcutaneous injections and subcutaneous or intramuscular implantations of benzo (a) pyrene (IARC, Vol. 3, 1973), dibenzanthracene (IARC, Vol. 3, 1973), 1,3-propanesultone (IARC, Vol. 4, 1974), dimethylsulphate (IARC, Vol. 4, 1974) and amitrole (IARC, Vol. 7, 1974) also give rise to local tumors." (Holmberg, S. 22–23.)

Dr. Holmberg concluded:

"The formation of local tumors by subcutaneous and intramuscular injections in the rat, together with evidence on mutagenic activity or on effects of DNA repair *in vivo* or *in vitro*, should be sufficient basis for regulating occupational exposure to that chemical. The complexity of a decision concerning the carcinogenic risk of chemicals is sometimes very great. Such decisions should therefore be made only by scientists who are specialists in the field of chemical carcinogenesis." (Holmberg, S. 25.)

The primary issue is not whether subcutaneous injection or subcutaneous implantation are direct parallels to human exposure, but whether positive results for tumor injection by these routes do or do not predict carcinogenic activity by other routes. The only extensive review of evidence on this point was provided by Dr. Tomatis, who presented an analysis of data reviewed by the IARC monograph Programme (Tomatis, 1977b; Appendix 4 to Tomatis Statement):

"Subcutaneous (S.C.) injection is often quoted as an example of an unreliable route of administration, particularly in rats. There are several good arguments to uphold the claim that the induction of local sarcomas following s.c. injection cannot be considered an index of the carcinogenic activity of the compound under test (Grasso and Goldberg 1966; Gangolli et al. 1967). We carried out a survey on a number of chemicals tested by the s.c. route in rodents to see if there was a correlation between their capacities to induce local and/or distant tumors in one species and their capacities to induce tumors by another route in another species.

"Of the 222 chemicals (excluding metals) considered in the first 11 volumes of the IARC Monographs (IARC 1972–1976), 114 had been tested by the s.c. route. Twelve of these had been tested by the s.c. route only and 102 by the s.c. and other routes. Of the 12 tested by the s.c. route only, one was negative (glycidyl stearate) and 11 positive. Of these seven (dibenzo[h,r,s,t]pentaphene, dibenzo[a,l]pyrene,2-(1-aziridinyl)ethanol, patulin, glycidyl oleate, propylene oxide, ethylene oxide) produced local tumors only, three (estradiol, progesterone, testosterone) produced distant tumors only, and one (tannins) produced local and distant tumors. Seven of these 12 chemicals were tested only

in the mouse, three only in the rat, one in both species, and one in the rat, the mouse, and the hamster.

"Of the 102 chemicals which had been tested by the s.c. as well as by other routes, 69 were found carcinogenic when the chemical was given s.c. or by another route, and for 18 chemicals the tests were negative or inconclusive regardless of whether the chemical was given s.c. or by another route.

"Nine chemicals tested by several routes of administration were found positive only when administered s.c. Of these, one (o-tolidine) produced only distant tumors, and the other eight (magenta, orange I, scarlet red, yellow OB, native carrageenans, parasorbic acid, penicillic acid, benzyl chloride) produced only local tumors. Seven of these nine chemicals were tested s.c. only in the rat, one in the rabbit and the rat, and one in the mouse and the rat. It must be noted that for only two chemicals (yellow OB and benzyl chloride) were the tests carried out by a route other than s.c. considered adequate negative tests. For the other seven, the tests, although negative, were considered inadequate or inconclusive.

"Six chemicals were negative when tested by the s.c. route and positive when tested by another route of administration. Of these, three (diazomethane, aramite, thiourea) were tested s.c. only in the mouse, one (mestranol) only in the rat, and two (para-aminoazobenzene and sudan II) in the mouse and the rat. Only the s.c. test with mestranol in the rat could be judged as an adequate negative test; the others, although negative, were considered inadequate.

"In conclusion, the administration of a chemical by the s.c. route produced what one could call false negative results for six (5.6%) of the 102 chemicals tested, and, if we accept all the criticisms of this route of administration, false positive results for nine (8.7%) of the 102 chemicals tested. Even, so, it appears that the s.c. route of administration is not much worse than any other route." (Tomatis, 1977b, p. 1350; Appendix 4 to Tomatis Statement)

Dr. Tomatis continued:

"It does not seem justified to exclude the subcutaneous route nor to ignore evidence of carcinogenicity from the induction of injection site sarcomas. Such a stand has some justification, but it should be better qualified. The subcutaneous route and the induction of local sarcomas can give very valid carcinogenicity evidence indeed. (see Tomatis, 1977, appended)

". . . too strict a reinforcement of the rule that the route of exposure for experimental animals should always be the same or similar to that to which humans are exposed could jeopardize a number of significant studies. To give an example, BCME was first found to be carcinogenic by topical application to the skin and by subcutaneous injection and only later on by inhalation." (Tomatis, S. 4–5)

and suggested:

"My suggestion is that the criteria for excluding a chemical from Category I, based on the presence or absence of similarity of the route of exposure, be applied with moderation." (Tomatis, S. 5)

Other witnesses also commented on this issue. Dr. Umberto Saffiotti (NCI) testified:

"An element of suspicion may well be raised by some topical implantation tests if previous studies and adequate controls should suggest that the effect may indeed be directly attributable to the chemical carcinogenic action of the test material. This was the case with the first experimental demonstration of the carcinogenic action of calcium chromate by intrabronchial pellet implantation, which induced bronchogenic carcinoma in rats (Laskin et al., 1970); this effect was later confirmed by the inhalation of the same chemical (Laskin and Sellakumar, 1974), which had already been linked to an occupational lung cancer risk by observations in man (reviewed in IARC, 1973)." (Saffiotti, S. 15)

Dr. Robert Squire (Johns Hopkins Univ.) commented:

"Another indication of carcinogenicity that has been excluded is the induction of tumors at sites of injection. This occurrence can assist in the evaluation of systemic or other data. Recently Tomatis (1977, p. 1350) demonstrated a high degree of correlation between the results of local subcutaneous carcinogenesis studies and animal experiments using other routes. Of 102 chemicals administered by subcutaneous as well as other routes, the results of 87 were similar. For 9 chemicals, results were positive by the subcutaneous route alone, reflecting an 8.7% 'false positive' rate. For 6 chemicals, results were positive by other routes but negative subcutaneously, reflecting a 5.6% 'false negative' rate." (Squire, S. 27)

Dr. Squire went on to recommend that OSHA use data arising from local tumor induction derived from injection or implantation routes of administration as supportive evidence for classification into Category I and that two such tests be deemed sufficient to support a classification of a substance as a Category II toxic substance. (Squire, S. 32).

Dr. Benjamin Van Duuren (NYU) commented:

"* * * the induction of skin carcinomas or sarcomas by exposure routes that do not parallel the primary exposure conditions in humans should not be considered 'grossly inappropriate.' " (Van Duuren, S. 6)

He went on to say that:

"Many people consider subcutaneous injection a valid test for solutions of chemicals when the doses used cause no local tissue damage or other toxic effects. This kind of test is different from physical carcinogenesis with solids implanted subcutaneously or suspensions injected subcutaneously which result in sarcomas only at the site of injection or implantation." (Van Duuren, S. 6)

Dr. Richard Griesemer (NCI) pointed out that:

"As I recall, it says in the regulation that induction of sarcomas at injection sites in rodents will not be used for regulatory purposes, and I wish to throw out for the record that we have examples of such experiments where we believe such findings are significant." (Griesemer, Tr. 975)

Dr. Benjamm Trump (Univ. of Md) and Dr. Curtis Harris (NCI) echoed the usefulness of subcutaneous injections. Dr. Trump commented:

"Yes, certainly, because with any route of administration there is likely to be distribution to various organs, and because of the factors already mentioned that modify organ distribution as a result of other exposure et cetera, therefore it is my opinion that the rules are also liberal on that point. Even subcutaneous administration when that has been followed in other tests where there have been claim of only subcutaneous neoplasms, it has been frequently discovered that other organs also show neoplasia." (Trump, Tr. 2007)

Dr. Harris commented further:

". . . I think there are a lot of people who would say that that sort of data would be important, and that generally it has been found by Tomatis and others in evaluating carcinogenicity data, that when it has been found subcutaneously, most frequently it will cause tumors elsewhere the compound will cause tumors elsewhere. So again, I think this is a point which, if I am correct in this, that the evaluation of results for regulatory decision are quite conservative." (Harris, Tr. 2007–8)

Dr. Umberto Saffiotti (NCI) supported the proposal as to subcutaneous injections:

"Experience in chemical carcinogenesis studies has shown that in a great variety of cases a chemical may affect different tissues or organs. Some carcinogens are reactive as such and produce their carcinogenic effect usually on the tissues with which they come directly in contact: these would include the upper digestive tract for oral intake (oral cavity, esophagus and stomach), the entire respiratory tract mucosa, from the nasal cavities to the lung, in the case of inhaled materials and the epidermal surface for skin exposure. These direct acting carcinogens may also produce their effects on internal organs if they are absorbed into the organism and distributed systemically to a variety of tissues. A striking example is provided by the effect of ethylnitrosourea in mice treated at birth by injection: as many as 60 different tumor types were induced, originating in almost all major organ systems (Vesselinovitch et al. 1974). An agent may however be administered by routes other than oral, respiratory or dermal in such a way that its localization is strictly topical and its effect is limited to the response of the exposed tissue, as in the cases of pellet implantations of non-diffusible materials in tissues or body cavities or of the implantation of plaques or disks into the connective tissues ("solid state carcinogenesis", see reviews by Bischoff and Bryson, 1964; Brand, 1975) There has been a wide consensus of scientific judgment that for such special cases the evidence may be insufficient for a

definition of potential human carcinogen, particularly if no comparable conditions of exposure exist in the human situation." (Saffiotti, S. 14–15)

Dr. Francis J. C. Roe (AIHC) cited examples of "non-specific carcinogenesis" as a predisposing factor to carcinogenic responses in animals exposed by inappropriate routes of exposure:

"Several years ago my colleagues and I reported the occurrence of tumours of the urinary bladder in mice following the implantation of glass beads into the bladder (Ball *et al.*, 1964; Roe, 1964). The prolonged presence within the bladder was associated with a variety of hyperplastic proliferative changes of the bladder epithelium as well as with the development of benign and malignant tumours. Our finding, which has subsequently been confirmed by others both in the mouse and in the rat, strongly suggest that prolonged non-specific irritation due to the presence of solid bodies in the bladder, such as calculi, are likely to predispose to tumour formation. If so then agents which, in very high doses, predispose to the formation of calculi in the urinary tract might be expected also to predispose to tumour formation. This is almost certainly the mechanism underlying the occurrence of bladder tumours in animals given high doses of ethylene glycol or polyoxyethylene(8) monostearate (Golberg, 1967). When these substances are fed in high dosage, rats excrete oxalate in such concentrations in the urine that oxalate stones form in the bladder. A few of the rats which develop such stones then go on to develop tumours of the bladder. A more recent example of the same phenomenon is the development of stones and bladder tumours in male mice fed diets containing 20% xylitol (unpublished data from studies still in progress). In neither of these instances did bladder tumours arise unless stones were also present." (Roe, S. 68–69)

On reviewing the evidence, OSHA recognizes the divergence of scientific opinion on this point, but is impressed by the evidence provided by Dr. Tomatis and other witnesses for the concordance between the induction of injection site tumors and other manifestations of carcinogenicity. Accordingly, although OSHA is unwilling to accept injection or implantation site tumors alone as sufficient evidence of carcinogenicity standing alone, OSHA believes that such evidence supports—and is in concordance with—other evidence that together meet the definition of a "potential occupational carcinogen". OSHA therefore believes that when such is the case, the total evidence warrants that the substance be classified as a Category I potential carcinogen. As we emphasize below, however, the caveat remains that when such results occur from physical, rather than chemical induction, such evidence will not be considered in the determination of a hazard to humans.

3. "Grossly Inappropriate", "Physical Induction" or "Solid-State Carcinogenesis"

The Surgeon General's "expert" NCI Ad Hoc Committee made the following recommendation in 1970:

1.a. Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard for man. Exceptions should be considered only where the carcinogenic effect is clearly shown to result from physical, rather than chemical, induction, or where the route of administration is shown to be grossly inappropriate in terms of conceivable human exposure. (NCI Ad Hoc Committee, 1970, p. 1 Exhibit 10(b) to Epstein Statement)

Unfortunately, the Ad Hoc Committee did not explain exactly what was meant by "physical . . . induction" or "grossly inappropriate" and comparatively little documented evidence on these points was presented in the hearing. Moreover, the NCAB Subcommittee explicitly excluded physical agents from consideration (p. 461).

However, what is clear from the Record is that special conditions of tissue exposure or reaction may result in a tumor response by mechanisms that appear due to physical rather than chemical properties of the test material. The Record indicates that the following conditions are evaluated differently in this respect:

a) The induction of sarcomas around a "solid state" implant of the test substance into a connective tissue shall generally not be considered an indication of the carcinogenicity of a substance when it is administered in another physical form.

b) The induction of a carcinogenic response by asbestos and other fibrous materials by a mechanism linked to certain physical characteristics such as fiber length and diameter is recognized as a basis for categorizing the exposure to such fibrous materials as a carcinogenic hazard.

c) The effect of particulate materials in the induction of respiratory neoplasms, when they are administered jointly with certain carcinogens (probably through their capacity to absorb and retain carcinogens, to penetrate the respiratory tract tissues, and to stimulate early cellular responses) is generally not recognized as evidence of carcinogenicity of these substances but rather as an indication of their role as cofactors in carcinogenesis; particulate materials require careful but separate consideration as a potential hazard.

d) The induction of a neoplastic response by a substance because of its radioactivity is recognized as a cancer hazard.

Thus OSHA does not intend to exclude from the scope of this set of regulations the induction of cancer by such agents acting as fibrous materials and/or dust, in view of the massive evidence for the carcinogenicity of asbestos. Moreover, OSHA is mandated to regulate occupational exposure to radiation, and at present does so under other regulations and intends to continue doing so. OSHA intends therefore to exclude only consideration of those routes and considerations of administration that give rise to what is known as "solid state carcinogenesis", namely the development of sarcomas from the fibrous tissue capsule formed around large and smooth-surfaced implants of a substance, especially when altering the physical properties of the implant's surface (e.g. comminution into small fragments or powder, perforation or roughening) abolishes the ability of the implant to induce sarcomas.

Several witnesses referred to this phenomenon of "solid state carcinogenesis", in which the implantation of relatively large masses of solid materials into the tissues of experimental animals leads to the induction of local tumors, depending on the physical characteristics of the implanted material (Saffiotti, S. 14–15; Roe, S. 68–69). OSHA believes that there is sufficient and substantial evidence in the record to justify discounting such results as clear indicators of carcinogenicity, and will not use such evidence in the classification of potential occupational carcinogens pursuant to this policy. For other cases in which there is a possible physical as well as chemical role in the mechanism of action of tested substances, e.g., for the biological effect of inhaled fine particles of poorly soluble substances, OSHA intends to examine the evidence carefully in the case-by-case rulemakings taken pursuant to this policy in the future.

C. OSHA's Conclusions

On the basis of an extensive review of the substantial evidence in the Record, OSHA concludes that its proposed position on this issue should be modified slightly. First, experiments involving any route of exposure in which tumors are induced or enhanced at sites distant from the site of administration should be regarded as providing relevant evidence of carcinogenicity. Second, experiments in which the substance under test induces only tumors at the site of injection or implantation as a result of its biological reactivity, the substance

should be regarded as providing at least suggestive or concordant evidence. Finally, however, if there is reason to believe that the tumors occur as a result of "solid state" carcinogenesis, OSHA will, at this time, regard the results as inappropriate to extrapolate to the human condition.

As detailed in the foregoing, OSHA will consider evidence for the induction of tumors in experimental animals to be directly relevant to the inference of potential carcinogenic risks to exposed workers in two sets of circumstances:

(a) If the animals were exposed via the oral, inhalation, or dermal routes, irrespective of the site where the tumors were induced;

(b) If the animals were exposed via other routes and tumors were induced at distant sites.

If animals are exposed via other routes and tumors are induced only at the site of administration (e.g. injection site sarcomas), OSHA will ordinarily consider such evidence only as "suggestive" evidence of carcinogenicity, or as concordant evidence which may support otherwise unconfirmed positive evidence in mammalian bioassays. OSHA however, will not consider such evidence even as concordant in cases exemplified by "solid state carcinogenesis," where evidence is provided that suggests that the induction of local tumors is related to the physical configuration or formulation of the material (e.g. the crystalline form or dimensions of a solid material, or the matrix of an impregnated implant). To be discounted by OSHA, such experimental results should be accompanied by evidence which indicates that the effect is produced *only* when the substance is administered in specific physical configurations or formulations. That is, at the least, negative results of adequately conducted experiments in which the same substance is administered in other configurations or formulations should be presented, and should be sufficiently well documented to support the argument for exclusion of the positive results.

Thus, OSHA's Cancer Policy provides (§ 1990.143(f)):

(f) *Routes of exposure.*

(1) Positive results in studies in which mammals are exposed via the oral, respiratory or dermal routes will be used for the qualitative identification of potential occupational carcinogens, whether tumors are induced at the site of application or distant sites.

(2) Positive results in studies in which mammals are exposed via any route of exposure and in which tumors are induced at sites distant from the site of administration will be used for the qualitative identification of potential occupational carcinogens.

(3)(i) Positive results in mammalian studies in which tumors are induced only at the site of administration, in which a substance or mixture of substances is administered by routes other than oral, respiratory or dermal, will be used as "concordant" evidence that a substance is a potential occupational carcinogen.

(ii) Arguments that such studies should not be relied upon will be considered only if evidence which meets the criteria set forth in § 1990.144(b) is provided.

And § 1990.144(b) states:

(2) *Tumors induced at site of administration.* Arguments that tumors at the site of administration should not be considered will be considered only if:

(i) The route of administration is not oral, respiratory or dermal; and

(ii) Evidence is provided which establishes that induction of local tumors is related to the physical configuration or formulation of the material administered (e.g., crystalline form or dimensions of a solid material, or matrix of an impregnated implant) and that tumors are not induced when the same material is administered in a different configuration or formula.

9. How Much Confirmation of Positive Results Is Necessary?

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA proposed, in general, not to identify or regulate a substance as a Category I Toxic Substance on the basis of a single positive result in an animal bioassay that was not "replicated. OSHA instead proposed to require confirmation of such a result, either by a second positive result in an animal test, or by positive results in short-term tests. OSHA discussed this issue in the Preamble as follows:

"For the reasons stated above, positive results in tests with experimental animals, if obtained under sound experimental conditions and with proper statistical confirmation, should in general, supersede negative results, including those in humans, as pointed out. In particular, positive findings of carcinogenicity in one animal species should generally outweigh negative reports in another, in relation to human application (UICC, 1969, p. 18; NCI, 1970, p. 2; NCAB Report, p. 9).

"Nevertheless, OSHA recognizes that 'false positive' results may arise occasionally, both through statistical accidents and honest errors in the conduct of single experiments. Accordingly, OSHA recognizes that much greater weight should be attached to positive results that have been replicated in another study than in a single unconfirmed result. As the National Cancer Advisory Board expressed the situation:

" 'Such increases [in neoplasms in experimental animals] may be regarded with greater confidence if positive results are observed in more than one group of animals or in different laboratories. The demonstration that the occurrence of neoplasms follows a dose-dependent relationship provides additional evidence of a positive result.' (NCAB Report, p. 5).

"While recognizing the importance of a single positive result as a warning flag, the Agency believes that it would not serve the interest of responsible public rulemaking to impose major, cost intensive regulatory requirements on the basis of unconfirmed, and possibly unreproducable [sic], results. Following the guidance of the NCAB Subcommittee, which emphasized in the above-quoted passage and elsewhere that varying degrees of confidence can be attached to positive results, OSHA proposes to establish a three-tier system of classification for those toxic substances that are found in the American workplace. In general, as is more fully discussed below, Category I toxic substances are those whose carcinogenicity, as defined, has been determined in humans or in two or more mammalian species of test animals or in one species if the results of that study have been replicated. Category II toxic substances are those whose carcinogenicity has been reported but the evidence for some reason is only suggestive, as defined, or positive in one species, but not yet replicated." (42 FR 54164–54165)

OSHA specifically directed the public's attention to this aspect of the proposal and asked for specific comments concerning it.

b. The Public's Response and OSHA's Evaluation

A number of comments was received on this aspect of the proposed regulations. Some witnesses and participants thought that positive results in at least two or more species should be required before regulating a substance at all; on the other hand, other participants thought that a single well-conducted test would suffice to categorize a substance as a full-blown carcinogen. A number of participants urged OSHA to make more explicit the concept of "replication". Other participants discussed the validity of using results in short-term tests as confirmation of evidence of carcinogenicity in animal bioassays.

The following is a sampling of some of those comments:

"Generally it is AIHC's position that in a regulation of this kind where interspecies exptrapolation is made, it is sound to have as basic criteria for OSHA Category I and AIHC Category II the requirement that the substance be shown to be carcinogenic in two mammalian species. The basic uncertainties in animal data discussed in the preceding sections of this brief point to the conclusion that it would be unwise as a general matter to rely on a single test in a single species for a generic classification scheme."

"We have addressed in the previous section the reasons why we believe it is important for OSHA, except in rare cases, to

require positive results in two species before classifying a substance in Category I. It is unsatisfactory to attempt to argue away the need for a two-species test by confirming 'replication' of a positive test in a single species. Should OSHA , despite the soundness of the view to the contrary, decide to rely on a single species, OSHA should require at minimum the confirmation of 'replication'. (NIOSH S. 5)

* * * * *

"As NIOSH points out, "simple replication using the exact same study design may not be particularly definitive." (NIOSH S. 5–6; *see also* Dr. Crampton S. 8.) It is imperative that if OSHA decides, incorrectly AIHC believes, to rely on replication of a test as confirmatory evidence, OSHA should clarify the ambiguous term "replication". The protocol or study design should be clearly defined. AIHC urges that OSHA adopt the NIOSH recommendations and require replication in a separate laboratory with separate controls. AIHC also recommends that a different strain and additional dose levels be required. If the route of administration is not the same as the route of explosure of humans, the replication should use the same route of exposure as humans." (AIHC Post-hearing Brief, pp. 159–160, 166–167)

Dr. Francis J. C. Roe (AIHC) discussed the concept of replication:

"Confirmation by replication is obviously not without value, and in circumstances where there is room to doubt the interpretation of a study because of defects in design or execution confirmatory studies are essential. However, the same experiment done twice with the same result doesn't resolve many of the kinds of problem[s] in interpretation discussed above. If a test substance non-specifically enhanced the incidence of virus-induced tumours in one experiment it is likely to do it again in a second similar experiment. *The second experiment confirms that an effect is produced by the test substance but it does not prove or confirm that the test substance is a carcinogen."* (Roe, S. 91–92, emphasis in original).

Dr. Johannes Clemmesen (Danish Cancer Registry) made a similar point:

"Replication within the same strain of mice is not equivalent with replication within a non-inbred species, not to speak of different species. It is not therefore a sound criterion for classification." (Clemmesen, S. 12)

Dr. Arthur Furst (Univ. of San Francisco) argued the need for confirmation in two species:

"There is a definite need to obtain positive results in more than one mammalian species before a determination of carcinogenicity can be made. OSHA proposes to accept as confirmation: (1) positive evidence in humans, (2) evidence in two or more mammalian species of test animals, (3) evidence in one species 'if the results of that study have been replicated,' or (4) 'the combination of positive result for carcinogenicity in a single bioassay in a mammalian test species.' Relative to (3) it is important to clarify on what basis replicate experiments will be an acceptable criterion of activity. Does this mean two experiments done in the same laboratory or done in two different laboratories? Must the animals come from the same supplier? Are the chemicals to be used from the same source? It seems to me that if chemical X is declared carcinogenic in specific YYY strain of rat by the OOO route, this information should be obtainable from different laboratories using YYY strain if rat when administering X by OOO route without requiring that only one source of the agent can be used.

"It would seem that replication by the same experimenters in the same laboratory using the same strain and the same experimental design would not be appropriate, for this would not detect any problems in the particular experimental design used or similar problems inherent in the procedures. Thus, it would seem that replication in a single species would require, at a minimum, that the experiments be carried out in a different laboratory or by a different group of experimenters, preferably on the basis of an independent design. Yet, I cannot feel comfortable with (3) alone and in my publications I will not call a metal, for example, carcinogenic without evidence in two or more mammalian species of test animals." (Furst, S. 18–19)

NACA suggested not only that positive results would be more persuasive in two species, but that the results should be replicated in each. Such a proposal would require four positive results before a chemical could be deemed carcinogenic:

"Not only may false positive effects, derived from statistical rather than biological considerations, be obtained in a first test species, but the same false positive effects could be observed in single test in a second species. For example, a putative carcinogen might be observed to have a higher incidence of bronchial neoplasms in male rats and endometrial adenocarcinoma in female mice. *More persuasive evidence of carcinogenicity would be provided if the same target organ were observed in both species.* In any case, the results in the second species like those in the first, should be replicated to exclude statistical artifact." (NACA, S. 47)

NIOSH expressed agreement with the need for some sort of confirmation of results in independent testing:

"A criterion for assigning chemicals to an OSHA Category I Toxic Substance is the necessity for replicated results. Replication may be achieved by obtaining a similar significant increase in tumor incidence in the same species where the experiments were performed with at least an independent set of control animals. Although we agree with the need for "replicating" animal experiments in order to include the substance in Category I (an exception might be made when highly significant results are obtained in an adequately conducted and biologically-appropriate test), we believe that simple replication using the exact study design may not be particularly definitive. We would hope that where researcher have the option, such confirming experiments would be performed in a different laboratory, perhaps using a different sex or strain of test animal, additional dose levels or a different route of administration so as to provide for a more comprehensive and accurate assessment of the substance." (NIOSH, S. 5–6)

In contrast to these comments, a number of witnesses expressed the opinion that confirmation and replication were unnecessary, and that a single well-conducted test would suffice to support a conclusion that a substance is carcinogenic. Dr. Bo Holmberg (Swedish NBOSH) presented this point of view:

"Concerning the classifiction of chemicals, OSHA takes the standpoint that a positive result in one single animal experiment should have less value than positive results obtained in two separate experiments or positive results obtained in two species. This standpoint may seem reasonable with respect to the possibility that false positive results in a cancer test may arise occasionally. It is however not very probable that a false positive result will be obtained (Page, 1977, Fears *et al.* 1977); even in a single animal test, should it be well performed. If a false positive result appears it does so only in remote cases and when high incidences of spontaneous tumors appear in the control series.

"The time required (at least 2–4 years) to obtain a second positive result may be sufficient to induce a number of additional cancers in occupationally exposed workmen. According to my opinion, one single well-done animal experiment in one species should weigh as much, in terms of regulatory measures, as two separate experiments or positive results from two species. Additional toxicological information, such as data on mutagenicity, biotransformation products, distribution of the compounds with known chemical and structure-activity relationships with other carcinogenic activity, of course adds to the weight of one single positive cancer test. I personally do not consider a few false positive results as being an important problem. I am generally more concerned with the false negatives, especially considering the inherent insensitivity of the conventional animal test systems. Positive results from one good conventional cancer test should thus be sufficient to initiate the most stringent regulatory measures. A positive result in one animal experiment should furthermore outweigh not only negative experimental data but should also outweigh negative epidemiological findings, for the reasons stated above." (Holmberg, S. 22–23)

The Environmental Defense Fund (EDF) argued that the requirement for replication should be replaced by a requirement for reproducibility:

"EDF notes that the preamble to the cancer policy states that a single, "exceptionally" well conducted test in one animal species may be considered sufficient for establishing

a presumption that a substance be classified in Category I. However, because, as a matter of public policy, the elimination of the risk faced by workers exposed to carcinogenic chemicals necessitates OSHA action without needless delay, EDF maintains that the present Section 1990.110(a)(4) be deleted and the following inserted in its place: "a single mammalian species if the results are reproducible." Reproducible results are defined as results obtained from an experiment that has been conducted and reported on in such a manner as to enable duplication of the experiment. EDF shares the concern expressed by the Subcommittee on Environmental Carcinogenesis of the President's Cancer Advisory Committee that a decision on the carcinogenicity of a compound not necessitate the actual replication of an experiment where the results of a single experiment clearly indicate a compound is carcinogenic.

"Because OSHA has no authority to require industry or other government agencies to test a substance, failure to enact the change suggested might result in years of continued worker exposure to a toxic chemical. For example, judging from past experience, the time between the acceptance of a recommendation to the National Cancer Institute (NCI) that a chemical be tested and completion of the tests is on the order of 5 years." (EDF, S. 2–3)

Dr. Lorenzo Tomatis (IARC) argued as follows:

"A single long-term experiment in a single species can be relevant if the experimental procedures were adequate and the results unambiguously indicated the induction of malignant tumors. Whilst confirmation of such a study can be advised, to wait for the confirmatory results of scientifically sound data might entail a delay in preventive measures. In addition, it is not clear which test(s), other than another long-term test, would be considered to add significantly to results obtained in a single long-term study carried out in a single species. This is of particular importance, since it is proposed that a chemical can be assigned to Category I if a positive result obtained in a single study in a single species is confirmed by a positive result obtained in a short-term test. The decision is apparently left to the Secretary, but it certainly entails a difficult evaluation of the significance of a variety of tests presently used. The so-called short-term carcinogenicity and related tests are certainly essential as a first screening of environmental substances, but there is no consensus as to which extent they can validate, or replace, results obtained in long-term testing. If it is assumed that a positive result in a short-term test can strengthen the results obtained in a long-term test, would negative results obtained in a short-term test weaken the results obtained in a single, long-term study? This point needs clarification." (Tomatis, S. 4)

EPA also disagreed with OSHA's proposed requirement for replication:

"EPA's policy does differ with OSHA's proposed regulation on one significant scientific issue. EPA is seriously concerned with the fact that the proposed regulations provide that animal test results generally cannot be relied upon as a sufficient basis for stringent regulatory action unless replicated or supported by short term studies. Although the proposal allows use of unreplicated animal tests if "exceptionally well conducted" we believe that this is too great a qualification. EPA policy is that an unreplicated test can be an entirely adequate basis for concluding that a chemical must be regulated as a carcinogenic risk. Such tests can often be extremely persuasive evidence that a hazard exists. Moreover, the delay while waiting for replication of tests may often be quite substantial." (EPA, S. 4)

Dr. David Rall (Director, NIEHS) emphasized the role of scientific judgment:

"On the one hand, there are cases where a single, well-conducted experiment giving clearly positive results should suffice to establish a chemical as a carcinogen and to justify stringent measures to reduce occupational exposure. On the other hand, there are cases where two or even three less conclusive positive results would still leave some doubt. The fact is that scientific experiments never give results that are 100% positive, nor 100% negative. Science deals in probabilities, and carcinogenesis biossays give results that may fall anywhere on a continuous spectrum of probabilities, extending from 2 or 3% at the lowest to nearly 100% at the highest. Division of this spectrum into discrete categories may be necessary for regulatory purposes, but it is necessarily arbitrary from a scientific point of view. Thus the recommendation of a scientist would be to make the criteria for categorization flexible, and to apply as much scientific judgment to each case as is compatible with legal and regulatory requirements.

"On the specific criteria proposed, there is no question that two positive tests provide greater confidence than one, even in the same species. There is no question that positive results in short-term tests (such as the Ames test, induction of unscheduled DNA repair, or malignant cell transformation *in vitro*) add to the confidence that one would have in a single positive animal test. This is not to say that these short-term tests are *equivalent* to lifetime bioassays in rodents: it merely reflects the fact that most carcinogens give positive results in short-term tests. Hence, if there is any reluctance to accept the result of a single animal bioassay, positive results in short-term tests would add sufficient evidence to overcome this reluctance. Certainly, it seems reasonable to use them in this way rather than to demand a second lifetime test in a rodent, which would be lengthy and expensive. In fact, most experts in carcinogenesis would be willing to accept the results of a single well-conducted test as definitive evidence for carcinogenicity (as indeed the IARC does in its monographs)." (Rall, S. 13–14)

Dr. Donald Kennedy (Commissioner, FDA) also emphasized the importance of the quality of tests:

"Very often it is the case that one good experiment with a lot of animals and very careful conditions, very carefully controlled conditions, is better than two experiments with minimal numbers. I often feel, for example, that in my own regulatory work, that I wish that more effort and more resources had been put into single experiments than into replications with equally inadequate numbers of the same experiments." (Kennedy, Tr. 502)

Other witnesses who expressed the opinion that a single well-conducted test that gave a clear positive result would suffice included Dr. Harold Stewart (NIH) (S. 5); Dr. Robert Squire (Johns Hopkins Univ.) (S. 25–26); Dr. Richard Griesemer (NCI) (S. 10–11); Dr. Benjamin Trump (Univ. of Maryland) and Dr. Curtis Harris (NCI) (Tr. 2003–2004); Dr. Renate Kimbrough (CDC) (Tr. 1786); Dr. I. Nathan Dubin (Medical College of Pennsylvania) (Dubin, Tr. 1197); Dr. Richard Bates (NIEHS; FDA) (Bates, Tr. 631); Dr. Samuel Epstein (Univ. of Illinois) (S. 39); and Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska) (S. 23).

Two exhibits were entered into the Record which discussed in mathematical terms the relative confidence that can be placed in replicated and unreplicated results. Dr. Robert W. Morgan (Univ. of Toronto) presented a paper by Morgan and Corey (1978) which formulated the probability that a substance is a carcinogen after considering results from carcinogenicity tests, the presumed sensitivity and specificity of these tests and an assumed *a priori* probability of carcinogenicity for the substance in question. The results of this paper are not very useful, however, because the *a priori* probability factor is extremely arbitrary and does not consider the relationship between sensitivity and the degree to which the treatment actually differs from the control procedure. A more sophisticated analysis of the problem is that by Fears *et al.* (1977), who showed that the probability of obtaining false positive results under the conditions of the NCI bioassay is reduced to a very low level by requiring replication *within* a single test, specifically by requiring a significant increase in tumors at the same site in the same species at *two* dose levels. For a fuller discussion of this analysis, see Section V.D. 5: *Statistical Significance.*

c. OSHA's Conclusions

On reviewing the evidence in the Record, OSHA is impressed by the fact that essentially no witness nor participant supported OSHA's original proposal, even semantically. A number of participants argued that positive results in two species should be required as a minimum requirement for any

inference of carcinogenicity. A number of other witnesses objected to the proposal that *replication* of results should suffice as confirmation, arguing that a result in an inappropriate species might be replicable although not biologically significant. On the other hand, an impressive body of expert opinion was presented to indicate that a single well-conducted test should suffice, and that to require replication or confirmation would unreasonably delay regulation of hazardous substances.

For reasons set out in Section V.D. 1 above, OSHA rejects the argument that positive results should be required in two species before an inference is drawn about human hazard or risk. The principal question to be addressed is how much confirmation is needed for a single positive result in one species.

The primary consideration which led OSHA to make its original proposal was that occasional false positives might arise in single unreplicated tests.The analysis by Fears *et al.* (1977) shows that the likelihood of false positives arising for statistical reasons can be reduced to an extremely low level if the statistical decision rules are chosen appropriately, with consideration of the spontaneous incidence of tumors at the site in question. This analysis, which was quoted extensively in Sections V.D.2 and V.D.5, shows that statistically reliable conclusions can be drawn from the results of single experiments (although in some cases the appropriate decision rules may require positive results in two or more groups of animals within the experiment). Thus, although OSHA will normally require some concordant evidence, as defined, before classifying a substance as a Category I Potential Carcinogen, OSHA is persuaded that positive results in single tests should be subjected to thorough scientific evaluation. As pointed out above, a number of distinguished scientists testified that a single test which gives a clear positive result should suffice for the identification of carcinogenic activity. This is particularly true if the positive result is extremely compelling—e.g., the induction of many unusual tumors, or the early deaths of most treated animals due to cancer. As pointed out by Dr. Tomatis (S. 4), Dr. Rall (S. 13–14) and Dr. Kennedy (Tr. 502), among others, such results may be fully valid if "the experimental procedures were adequate;" or if the test is judged to be "well-conducted." For these reasons, OSHA is providing in § 1990.112(a) that a substance may be classified as a Category I Potential Carcinogen on the basis of scientifically evaluated positive results.

. . . . in a single mammalian species in an adequately conducted long-term bioassay, in appropriate circumstances where the Secretary determines the requirement for concordance is not necessary.

OSHA's intention is that this provision should only be used in cases where the evidence has been carefully scrutinized and found to be unusually compelling. For reasons stated elsewhere in this preamble (Section V.D.11) it is not possible to establish specific criteria for the judgment that a test is "adequately conducted" and that the results are "positive". As in other cases, the principal need is for the exercise of good scientific judgment in the evaluation of data.

OSHA believes that its position on this issue is similar to that recommended by the Food Safety Council:

"The outcome of a chronic animal test may be regarded as positive if clear evidence of neoplastic or non-neoplastic toxic effects is obtained, as judged by end-points that may be clinical, pathological or biochemical. Circumstances in which such positive evidence is obtained may include a similar result in a different animal species or in a separate experiment with the same species, recognizing the possiblility of one experiment yielding erroneous conclusions. In the case of a single experiment with one animal species, the evidence may also be sufficiently compelling to exclude the likelihood of a false positive. Examples would include the induction of rare tumors or diseases, evidence of dose-related response in two or more dosage levels, positive results in both sexes, or in the case of animal carcinogenicity, positive evidence for genetic toxicity as described in Chapter 6." (Food Safety Council, 1978, p. 107)

10. Can "Safe" or "No-Effect" Levels Be Set For Exposure To Carcinogens?

a. OSHA's Proposal

OSHA proposed (42 FR 54167, 54185) that substances deemed to meet the definition of Category I Toxic Substances, by the previously mentioned criteria, would be regulated to the lowest feasible level of employee exposure, as determined by the Secretary of Labor.

This position was proposed because of the scientific evidence discussed in the preamble to the proposed set of regulations that "safe", "no-effect", or "threshold" levels of exposure could not be objectively established for carcinogens for any individual and certainly, not with respect to any given human population. And, in the event that such levels do characterize any or all carcinogens for all persons, OSHA did not believe it possible to determine these levels exactly nor practicable to estimate them precisely. For the purposes of regulation, therefore, OSHA proposed that it was necessary for regulatory purposes to assume that "threshold", "safe" or "no-effect" levels could not be established. For this reason OSHA proposed to establish its future standards for exposures to individual carcinogenic substances at the lowest feasible levels for all substances identified as Category I Toxic Substances.

b. The Public's Response and OSHA's Evaluation

A number of scientific witnesses expressed general support for OSHA's position. Dr. Richard Bates (NIEHS; FDA) commented:

"One of these assumptions is that there is no threshold below which exposure to a carcinogenic chemical entails no risk. That is to say, although decreasing the exposure will decrease the risk of cancer induction, there is no level below which the risk becomes absolutely zero until zero exposure is reached. Debate over this question is partly a matter of semantics or definition of terms. Some scientists approach this issue as a mathematical problem by which the likelihood of induction of cancer becomes very, very small as exposure becomes very, very small, but the possibility still remains. Others will conclude that when the risk gets small enough it is the practical equivalent of zero. Thus, the first group might argue that a risk of one in one billion of inducing cancer is a finite (though perhaps tolerable) risk and not a threshold while the other group may argue that for practical purposes this is so low as to be the practical equivalent of a threshold. More scientific arguments for threshold may point out the possibility that chemicals are metabolized differently at high exposure levels than at low levels, that protective mechanisms may be more effective at low exposure levels than at high ones, and that repair mechanisms may be more effective at low exposure levels than at high levels. In principle, these arguments can only be used as arguments in favor of a threshold if it can be shown that the carcinogenic metabolite present at high exposure levels is totally absent at low exposure levels (rather than simply present as a lower proportion of total metabolites), or that defense and repair mechanisms are totally effective (rather than proportionately more effective) at low exposure levels in contrast to high levels. In the absence of this information as a general principle or for any specific chemical under question, these arguments may suggest that the risk from low levels of exposure may be somewhat less than otherwise might be projected from high exposure experiments, but they fail to provide convincing arguments for the general concept of threshold." (Bates, S. 13–15, references omitted)

Dr. Donald Kennedy (Commissioner, FDA) commented:

"A second scientific issue that I think requires comment is that relating to the matter of "safe" levels of human exposure to carcinogens. As a scientist I must hold to the view that it may some day be possible, once the mechanisms by which carcinogens exert their effects are well understood, to establish procedurec for estimating levels of carcinogen exposure that represent no risk to humans. For the present the best available information on this subject leads me to the conclusion that scientists do not have the knowledge to permit such estimations. We must for the present hold to the view that some health risk exists at any level of carcinogen exposure." (Kennedy, S. 10–11)

Dr. Marvin Schneiderman (NCI) cited several NAS committees whose conclusions concurred with the OSHA proposal:

"Anticipating a later remark by Sidney Weinhouse in the Cold Springs Habor Symposium on the Origins of Human Cancer (Book C. p. 1308), Cold Springs Harbor Laboratory, 1977, and the conclusions of the anonymous authors of the "Drinking Water and Health" and "Contemporary Pest Control Practices and Prospects:

"Another problem, and one which unfortunately is not amenable to scientific solution, is the existence of a threshold. Is there a lower limit of exposure below which normal repair and recuperative processes will prevent cancer? This is perhaps one of the most pernicious questions that confront the regulatory agencies. It is the refuge of the apologist for industry and has support from traditional toxicology. However, there is as yet no evidence whatsoever that thresholds exist for the irreversible process of carcinogenesis. If they do exist, they would be at a nondeterminable low level, and they would probably differ for each substance and for each test species. It is important to recognize also that carcinogenic risks to man have to be weighed against a substantial background of an already existing environmental as well as probable endogenous cancer burden, which more than likely has already exceeded any threshold which might exist. (Crump et al. 1976). For these reasons, prudence requires the assumption that thresholds for carcinogens do not exist. Unless some new, compelling information appears, the concept of threshold serves no useful purpose in regulatory decisions. The authors assumed that no threshold could be demonstrated for carcinogens". (Schneiderman, S. 26–27)

Dr. Matthew Meselson (Harvard Univ.) presented this issue in his oral testimony:

"It is conceivable, but my belief is that it should be assumed in general that there is no such thing as a threshold. I have three reasons for this. And by the way, none of these three reasons is the reason which is a further reason you could use, but I do not, used by my colleague, Dick Wilson, who says it is the most conservative, generally reasonable hypothesis. I do not take that—I do not use conservatism as my choice.

"But the first is that I know of no publication in the entire literature on dose response of primary carcinogens that provides evidence for the existence of a threshold. I have asked toxicologists to send me publications with such evidence, and I have not received a single one. I have gone through the— as mentioned in the National Academy report that is part of my testimony—the dose response study by the Franklin Institute done under contract with the National Cancer Institute, in seeing there not a single case, and they have tried to review the entire world literature on dose response, 150-some odd dose response curves are reviewed in that study. I have not seen a single case in which the data depart significantly from either the probit or single particle hypothesis in a way demanding a threshold.

"More than that, one has to remember a very simple but for some reason until the last few years overlooked point, and I think a very powerful point, and that is as animals we humans are way past the threshold. We are like an experiment with mice or rats in which 25 percent of them are coming down with tumors. We are not a cancer-free population. We have an enormous incidence of cancer in our population. So that unless one is talking about a chemical which is being activated by an absolutely unique pathway unique to that chemical, an activating enzyme that does not work on anything else, or does something unique to the entity that no other chemical does, activates a mutagenic repair pathway that no other chemical does, unless that is the case, we are just talking about adding a little bit more when we talk about low dose, to what is already a lot, and demonstrably past the threshold, because we are already past any thresholds as a population.

"So to take the burden on one's self of saying that I believe this chemical is unique in the world, is operating by a mechanism that is not already going on in our bodies, is an incredibly arrogant statement. There would be no basis in sicientific fact for such an a priori statement. So it would be different if nobody ever got cancer, and some scientists came along and said, we have just discovered that there could be a disease if you let this certain thing in the environment. We are going to call it cancer. Then somebody could say, but how do you know there is not a threshold for this hypothetical disease that at present nobody is getting, because if nobody is getting it, clearly we could be below the threshold. That might be why nobody is getting it. But if 25 percent of us are getting it, you have to make some, in my opinion, very far out assumptions before you can conclude that a chemical under—a particular chemical under scrutiny is going to operate in such a way as to not already be past that hypothetical threshold.

"And then finally, the most plausible biological models for the—and here we are in an area of more theory, but to me the most plausible biological models for carcinogenesis do not involve mechanisms that would admit of a threshold.

"So I see no basis at all for any policy assumption of a threshold. You cannot say where it is, even if it were there. The strong theoretical argument is to believe that if there were one we are out past it anyway. And there are even strong arguments, I believe, for saying there is not one in most cases.

"Now, does this mean that you could not someday come up with some chemical or some imagined pathway that would have threshold-like characteristics? No. But it does mean that for your average chemical that you have to think about, a new chemical, or a chemical that has been in use, it seems to me that the overwhelming burden of all the arguments is that you must assume that there is no threshold." (Meselson, Tr. 1544–1547)

Dr. Samuel Epstein (Univ. of Illinois) presented extensive evidence in support of OSHA's position (S. 28–33) citing the IUAC in 1954 and 1956, HEW Secretary Flemming in 1960, and the "expert" Ad Hoc Committee of the Surgeon General in 1970. He asserted in cross-examination:

"I assert that there is no method of setting safe levels for chemical carcinogens." (Epstein, Tr. 1393)

Dr. David P. Rall (Director, NIEHS) opened his oral testimony with a comment which put matters in perspective:

". . . [A]lthough theoretically no-effect thresholds may exist for carcinogens, the threshold concept is presently inapplicable to the human population in the United States. Since 16% of our population now dies of cancer, I submit that as a population we have now exceeded any theoretical population threshold." (Rall, Tr. 354)

Dr. Harold Stewart (NIH) quoted the minutes of the Ad Hoc Committee on Testing for Environmental Chemical Carcinogens of which he was chairman:

"In the case of the human population, with the completely unknown variations in sensitivity to any chemical carcinogen, and with the impossibility of knowledge of other variables that may affect responsiveness to these agents, attempts to establish threshold levels for carcinogenicity are unrealistic." (Stewart, S.3)

Dr. William Nicholson (Mt. Sinai School of Medicine) commented:

"Despite considerable research on the effects of carcinogenic substances and their dose-response relationships, no data exist that would define a threshold for any carcinogen. The task confronting one who would define a level below which no carcinogenic risk exists for human populations is virtually an impossible one." (Nicholson, S.1)

Mr. Richard Peto (Oxford Univ.) introduced a paper into the Record which:

". . . argues that what should in general be expected from chronic low exposure levels is that, because of the (frequently ignored) effects of the general background of carcinogens, no safe threshold doses will exist." (Peto, S.1)

Other witnesses who supported OSHA's position on this issue include:

EPA, S.3; Dr. William Lijinsky (NCI—FCRC), S.31; Dr. Robert Squire (Johns Hopkins University) S.22; Dr. Benjamin Van Duuren (NYU), S.9; Dr. Bo Holmberg (Swedish NBOSH), S.14; Dr. David Hoel (NIEHS), S.1; Dr. Lawrence Fishbein (NCTR), Tr. 1873–1874; Dr. David Wegman (Harvard Univ.), Tr. 1674; and Dr. Arthur Upton (Director, NCI), S. 6–8.

In addition to the reports cited in the proposal, several other reports of expert committees were introduced into the Record which provided additional general support for OSHA's proposed position. For example, the National Academy of Sciences Report on Pest Control (1975a) described the issue as follows:

"*Threshold hypothesis.* This hypothesis assumes that there is a dose below which cancer induction cannot occur. An examination of published dose-response data for chemical carcinogenesis in laboratory animals provides no clear indication of a threshold for any carcinogen (Craig and Miller 1974). In a review of 151 dose-response curves, none was found to be clearly inconsistent in a manner suggesting a threshold with both the single-event and the probit hypotheses discussed below. Neither is there any adequate theory of chemical carcinogenesis that would require the general existence of thresholds. Thus, even if a threshold is postulated, there is presently no empirical or theoretical basis for determining the dose at which it may occur. Unless and until this can be done, the threshold concept does not provide a practical basis for risk estimation." (NAS, 1975a, p. 83, Exhibit H to Rall Statement)

Another Committee of the National Academy of Sciences, charged with evaluating the potential carcinogenicity of the pesticides heptachlor and chlordane, reported as follows on the issue of thresholds and "virtually safe level of exposure":

"*Question IV:* If chlordane or heptachlor or their metabolites pose a carcinogenic risk to man, is it possible to determine a level of exposure to chlordane or heptachlor or their metabolites which does not pose a risk of cancer to man or which constitutes a virtually safe level of exposure?

"*Answer:* Neither statistical nor biochemical procedures permit determination of a threshold dose for any carcinogen. Furthermore, since the committee believes that there are not sufficient data to permit a reliable estimate of the magnitude of risk to humans from these pesticides, it is unwilling to propose a virtually safe level of exposure.

"*Discussion:*

The first part of Question IV asks, in effect, if thresholds exist for agents that pose carcinogenic risks to humans. This question has been considered in depth by the many experts and expert committees referred to in the discussion on Question II. Their conclusions indicate that it is not known if true thresholds exist in the carcinogenic responses of humans and laboratory animals to chemical carcinogens. Even if they do exist, there are no data for humans that would permit the estimation of threshold concentrations of chlordane, heptachlor, or their metabolites. Nor is it possible to calculate such threshold concentrations for humans from the carcinogenicity data obtained from tests with laboratory animals because of the uncertainties inherent in the extrapolation of such data from one species to another.

With regard to the second part of Question IV, it is impossible to guarantee noncarcinogenicity of a compound in animals or humans. Furthermore, the determination of a "virtually" safe dose requires knowledge of the dose-response relationship in humans and the specification of an acceptable risk. The committee is of the opinion that knowledge of the carcinogenicity and metabolism of these compounds is inadequate for the prediction of dose-response relationships in humans and that the determination of acceptable risk would be a societal judgement and not one based on scientific facts. "(NAS, 1977b, pp. 31–32; Appendix 10d to Epstein Statement). (Footnote omitted)

A third Committee of the National Academy of Sciences, reporting in 1977 to EPA on *Drinking Water and Health,* provided an extensive discussion of thresholds in the context of risk assessment for carcinogens in drinking water. This Committee formulated four principles "that underlie efforts to assess the irreversible effects of long-continued exposure to carcinogenic substances at low dose rates." Principle 2 reads as follows:

"Methods do not now exist to establish a threshold for long-term effects of toxic agents" (NAS 1977a, p. 54; Appendix I to Rall Statement).

In support of this principle, the Committee provided an extensive discussion of the scientific evidence for low-dose effects of carcinogens. This discussion read in part as follows:

"Whether or not a particular effect follows a dose-response relationship that has a threshold depends entirely on the mechanism of the effect. Many effects have thresholds. For example, the gastrointestinal-radiation syndrome, acute drug toxicity, and radiation or drug control of some tumors all have dose-response curves that show thresholds. The curves are sigmoid, and below a particular dose there is zero probability of producing the effect, because it requires many independent occurrences and will not occur until the number of such events exceeds some critical value. The gastrointestinal-radiation (or drug) syndrome is a case in point. An animal will not die until the number of intestinal crypt cells that have been killed exceeds some value that is critical to the integrity of the organ. Any radiation or drug dose that kills fewer cells than this critical number can be considered to be "safe" (at least for this one syndrome).

"We are used to thinking in terms of thresholds and sigmoid dose-response curves. For example, if it costs $4,000 to buy an automobile, we do not imagine that we will have a 50% chance of buying the same vehicle for $2,000. If 100 aspirin tablets constitute a lethal dose, we do not calculate that we will have a 1% chance of dying if we swallow a single tablet. Because we know the mechanisms underlying these events, we expect thresholds to the dose-response curves, and indeed they are evident.

"However, other effects may well not have threshold dose-effect relationships. If an effect can be caused by a single hit, a single molecule, or a single unit of exposure, then the effect in question cannot have a threshold in the dose response relationship, no matter how unlikely it is that the single hit or event will produce the effect. Mutations in prokaryotic and eukaryotic cells can be caused by a single cluster of ion pairs produced by a beam of ionizing radiation. We would expect that mutations can be caused by a single molecule or perhaps group of molecules in proximity to the DNA. The necessary conclusion from this result is that the dose-response relationship for radiation and chemical mutagenesis cannot have a threshold and must be linear, at least at low doses.

"It is one step further to correlate mutagenesis with carcinogenesis. Nevertheless, the evidence is strong that there is a close relationship between the two (McCann et al., 1975; McCann and Ames, 1976; Ames. 1976; DHEW, 1977).

"We therefore conclude that, if there is evidence that a particular carcinogen acts by directly causing a mutation in the DNA, it is likely that the dose-response curve for carcinogenesis will not show a threshold and will be linear with dose at low doses.

Consideration of the Dose-Response Relationship

"In considering the possibility of thresholds for carcinogenesis, it is important to understand that there is no agent, chemical or physical, that induces a form of cancer in man that does not occur in the absence of that agent. In other words, when there is exposure to a material, we are not starting at an origin of zero cancers. Nor are we starting at an origin of zero carcinogenic agents in our environment. Thus, it is likely that any carcinogenic agent added to the environment will act by a particular mechanism on a particular cell population that is already being acted on by the same mechanism to induce cancers. This reasoning implies that only if it acted by a mechanism entirely different from that already operating on the tissue could a newly added carcinogen show a threshold in its dose-response curve.

Examination of Experimental Dose-Response Curves

"The most extensive information on carcinogenesis both in experimental animals and in humans is with ionizing radiation (BEIR, 1972). Although there is evidence implicating thresholds in some animal tissues (Walburg, 1974), thresholds have in general not been established for most tissues. If such thresholds exist, they occur at sufficiently

low doses that it would require massive, expensive, and impracticable experiments to establish them. In view of the common finding—for example of a linear dose-response relationship (unaffected by dose-rate)—for cancer induction in animals by high LET radiation, it is unlikely that such thresholds exist. Linearity is not essential to the no-threshold argument since nonlinear, dose-response relationships do not necessarily imply the existence of thresholds.

"Recent reviews by Bardensen (1975) and Brown (1976) suggest that the dose-response curve for mutation induction, the production of chromosome aberrations, and the induction of tumors in mammals is linear with low-LET radiation up to about 50–100 rads. Brown (1976) concluded from the available human data that this also applies to man. Such findings argue against a threshold for ionizing radiation. Because many carcinogenic agents act like radiation in producing mutations, chromosome aberrations, and cell killing, we see this as an additional argument against the likelihood of thresholds in the dose-response curves of these agents.

Heterogeneity of the Population

"The human population in the United States—the population we are trying to protect—is a large, diverse, and genetically heterogeneous group exposed to a variety of toxic agents Genetic variability to carcinogenesis is well documented (Strong, 1976), and it is also known that individuals who are deficient in immunological competence (for genetic or environmental reasons) are particularly susceptible to some forms of cancer (Cottier et al., 1974). It seems, therefore, that even if we were to postulate an average threshold for a particular cancer induced by a particular agent, we would in practice need a series of thresholds for different individuals. It would be extremely difficult to establish a single threshold.

"We conclude from these arguments that, despite all the complexities of chemical carcinogenesis, thresholds in the dose-response relationships do not appear to exist for direct-acting carcinogens. If they do exist, they are unlikely to be detected and, hence, impossible to use. This means that there can be no totally "safe" exposure to a particular carcinogen, nor can the term "margin of safety" have any meaning. Any dose of a carcinogen must be considered to be associated with a risk, and even if that risk is vanishingly small, it must be estimated."

* * * * *

"Even if a normal cell has been transformed to some intermediate stage in the carcinogenic process, this would not necessarily mean that cancer must occur. Cell repair or recovery or some other response from the immune mechanisms may be sufficient to stop or reverse the process before the final stage is reached. In addition, the death of these transformed cells may occur before the process has a chance to continue toward the eventual cancer. This is one of the major arguments in favor of the existence of a threshold. However, if there is some probability that these recovery mechanisms will not complete their role before the occurrence of another event or transformation, this type of threshold will not exist.

"Thresholds may be considered from two viewpoints—an "actual" threshold, which is an exposure below which any carcinogenic response attributable to the specific agent is impossible, and a "practical" threshold, which is an exposure below which an attributable carcinogenic response is highly unlikely. In discussing carcinogenic thresholds, Mantel (1963) has argued that it is immaterial whether or not "actual" thresholds exist, and that one should consider the "practical" thresholds when estimating human risk. Mantel and Bryan (1961) stated that a risk of cancer of 1 in 10^8 could be thought of as a "practical" threshold and that efforts should be made to estimate exposures that would produce no more than this risk. Using mathematical models that relate the latency period (time between initiation of exposure and appearance of cancer) to the exposure, Jones (1976) suggested that a "practical" threshold could be defined as an exposure for which the latency period is beyond the normal life span.

"Experimental or observational evidence of the existence of an "actual" threshold is usually presented in the form of a dose-response graph, in which the percentage of animals with tumors or the average number of tumors per animal is plotted against the dose of the carcinogen. Either the existence of doses that do not lead to an increase in tumor incidence over controls, or the extrapolation of such curves to low doses that apparently would result in no tumor increase, is cited as an indication of the existence of a threshold below which no response is possible. This type of reasoning is an exercise in self-deception.

"In the first case, failure to observe positive responses does not guarantee that the probability of response is actually zero. From a statistical viewpoint, zero responders out of a population of size N is consistent at the 5% significance level with an actual response probability between zero and approximately 3/N (e.g., when N = 100 and zero responders are observed, the true probability of response may be as high at 3%).

"In the second case, when an observed plot of dose against tumors is extrapolated downward to find a no-effect dose, it is assumed that the observed dose-response relationship, usually linear, will obtain throughout the entire spectrum of doses and that one threshold exists for the entire population at risk. The assumption of linearity throughout the entire dose spectrum can easily lead to erroneous conclusions. For example, consider the true dose-response relationship shown by the dashed curve in Figure II–I.

"The curve is convex, which would be consistent with a multievent theory of carcinogenesis in which more than one event is affected by the carcinogenic agent. This type of convex dose-response relationship, when sampled in an animal experiment over only a part of the dose range, could be thought to imply the existence of a threshold if simple linear extrapolation is used. If the animal experiment is performed at doses between A and B, one could conclude that a threshold exists at dose d_1; if the experiment is performed at doses between B and C, the conclusion could be that a higher threshold exists at dose d_2. In fact, with convex dose-response curves, simple linear extrapolation will always imply the existence of a threshold, if the experiment is performed over any range of doses that appears to produce linearity between dose and response.

"In addition, the assumption of one threshold is unrealistic. It is much more likely that, if thresholds do exist, not all members of the population have the same one. The human population is a very diverse, genetically, heterogeneous group that is exposed in different degrees to a large variety of toxic agents. Many different disorders may affect the frequency of mutational events in specific tissues. Disorders characterized by chromosomal instability have been found to be predisposed to malignancy. Patients with xeroderma pigmentosum are highly susceptible to ultraviolet-induced skin cancer, and it has been found that they have deficient DNA repair mechanisms (Robbins et al., 1974). In Bloom's syndrome, there is an immune deficiency and increased risk of leukemia and cancer of the colon (German, 1972). These systems may provide a model in which the risk of mutation and subsequent malignancy after exposure to an environmental carcinogen may be genetically determined. If malignancy is the result of a series of mutational events, there must be subpopulations at various degrees of risks or with various thresholds for the carcinogenic agent. Therefore, the search for thresholds should not be a search for one specific no-effect dose applicable to all members of the population at risk; rather, the problem is to find many thresholds for each of the subgroups within the population." (NAS, 1977a, pp. 37–44; Appendix I to Rall Statement).

c. Areas of Confusion Presented in the Record

A large number of witnesses presented testimony on the subject of thresholds or no-effect-levels for carcinogens. Many witnesses expressed general support for the OSHA position or provided additional details on specific points; other witnesses either objected to the OSHA proposal in general terms or proposed specific reasons why it should not apply in certain individual cases. However, some of their testimony appears to have reflected confusion over terminology or scientific concepts. It is important to resolve this confusion before analyzing the evidence on the principal points at issue.

First, the distinction between a "no observed effect level" or "no effect level" (NOEL or NEL) and a "threshold" was frequently blurred. For example, Dr. Paul Kotin (Johns-Manville) stated in his written submission:

"Chemical carcinogens can be administered at dose levels that yield no

cancers in laboratory animal models and that neither shorten the animals' life span nor results in demonstrable abnormalities in metabolic and physiologic capabilities. This is clearly a no effect (threshold) level." (Kotin, S. 13)

and in his oral presentation:

"I do not know how you define threshold, so let us avoid that; but I hope you will accept no effect level as a euphemism for it for our discussion." (Kotin, Tr. 4905)

Drs. P. J. Gehring and G. E. Blau in their article, "Mechanisms of Carcinogenesis: Dose Response" stated:

"Biologically, "threshold" has been interpreted to mean that there is a dose below which no response will occur. Hence when a dose is found that did not produce a toxic response in a reasonable number of subjects, laboratory animals or humans, it is assumed that the dose is subthreshold." (Gehring and Blau, 1977, p. 165; Exhibit 9 to Hoel Statement).

Dr. Robert Olson (St. Louis Univ.) disposed of the issue by defining threshold to be synonymous with no-effect level:

"Threshold" is an operational term denoting the highest dose at which no measurable effect occurs. No-effect levels have been repeatedly demonstrated for carcinogens in animals and man." (Olson, S. 10)

For scientific or regulatory purposes, *threshold* would be a dosage level below which an effect (cancer) *could not* and *never would* occur, not merely a point below which an effect would be infrequent, no matter how very infrequent. The National Academy of Sciences in their report, "Principles for Evaluating Chemicals in the Environment" cited by Mr. Sheldon Samuels (AFL–CIO) noted:

"The term "no-effect level" is statistically meaningless, and therefore of limited value, since it merely means that no effect was observed in studies using a group of animals of particular size." (Samuels, Tr. 7263)

Thresholds may hypothetically exist at the cellular, individual, or population levels. It was often unclear exactly what type of threshold was being discussed in the written statements and oral testimony. Occasionally, arguments developed from a biochemical basis were generalized to the population level without due consideration of all the potential complications.

Dr. Paul Kotin (Johns-Manville) observed that there is a "series" of thresholds, in his oral responses to the following question:

"Q. "Our understanding of chemical carcinogenesis at the molecular level is so primitive as to make the question of a threshold almost premature. Would you agree with that statement?

"A. It even sounds familiar. I might even have written it.

"Q. Yes. In fact, you did.

"A. Yes, I know. I have to elaborate very briefly here. You see, the question of a threshold, there are series of successive thresholds, and what I was speaking [of] there was the kinetics of the interaction between an environmental agent, a molecule of beta naphthylamine, whatever it is in a chlorinated hydrocarbon or whatever it is in a fiber that initiates the change with the genetic material. This is what I had in mind; that the threshold there we really know nothing about." (Kotin, Tr. 4903)

The determinants of a cellular threshold alone would be very complicated, as explained by Dr. R. W. Hart (Ohio State Univ.) in his written testimony:

"There are four general categories of DNA repair in mammalian cells: a) excision or prereplication repair, b) strand break repair, c) postreplication repair, and d) photoreactivation. It is now apparent that the first three of these are composed of multiple pathways. However, little is known concerning the specific enzymology, kinetics, or biological consequences resulting from alterations in these pathways. Additionally, DNA repair is a dynamic process in which: 1) various repair mechanisms coexist, 2) the state of the cell cycle may favor one repair system over another, 3) the state of differentiation of a given tissue may play a role in the extent and type of DNA repair that predominates, and 4) the biological manifestations of the type and/or quantity of repair or lack thereof may vary as a function of the aforementioned factors." (Hart, S. 15–16) (Footnotes omitted)

Dr. Richard Bates (NIEHS; FDA) discussed the intricacies of this question at some length in his written submission:

"The science of toxicology will have made immense strides when it becomes able to use the results of animal experiments to precisely predict the toxic risk of a chemical to any individual or group of humans. Unfortunately we are not there yet. The problem is terribly complicated. Absorption, rate of metabolism, and excretion of environmental chemicals may differ among species. Species may differ in the types or relative ratios of metabolites formed from any chemical and in the sensitivity of various organ systems to the toxic effects of these chemicals. Individuals within each of these species may show wide differences among these parameters depending upon their genetics and on modifying environmental circumstances. Susceptibility in the same individual may fluctuate during the phases of various biological cycles. Although we know these variables exist, we do not have enough knowledge to weigh each of the factors in any particular case and come up with a reliable multiplier for converting results of animal experiments to risk for any individual human under his or her conditions of life."

* * * * *

"The concept of threshold is also confused by some scientists using the term to apply to individuals while others use it to apply to populations. As discussed earlier, the sensitivity of any individual to a chemical carcinogen will vary depending upon his genetics, his state of health, age, and exposure to a wide variety of environmental factors. Thus more resistant individuals may be able to tolerate an exposure level that would result in cancer for the more susceptible. One way of thinking of threshold would be to define this level as below the threshold for carcinogenicity of the first individual but above that for the second.

"When these considerations are applied on a population basis, it can be seen that this level might increase the total incidence of cancer in a large exposed population even though the level might be one that could be tolerated by many individuals within it. Since approximately a quarter of the American population will develop some form of cancer during their lifetimes, it is apparent that many are already over their threshold and additional exposures are likely to push more over that limit.

"At the present time, we are still in a position of being unable to unequivocally decide whether or not thresholds exist, as defined at the molecular or population level, or to determine which individuals in the population may or may not be able to tolerate additional exposure from carcinogenic chemicals." (Bates, S.9, 15).

Dr. David Rall (Director, NIEHS), in response to a question about whether other scientists may adopt assumptions which may lead to the prediction of thresholds, commented:

"It is very interesting. I am really not aware of any other scientists who have explicitly doubted or considered population thresholds. The discussion that I have seen and read deals with individual thresholds, but I have not seen discussion doubting the fact that for populations, there probably are no thresholds." (Rall, Tr. 455)

Later he clearly expressed the differences between a population threshold and an individual threshold:

". . . there are variations in the way chemicals are activated in the body to become carcinogens, and the mechanisms the body has to inactivate those chemicals. There are immunological mechanisms which may or may not serve to rid the body of newly-developing cancers. In looking at a very clean animal population, you can conceive that the first little bit of a chemical that is carcinogenic may be totally detoxified by these and other mechanisms. But they all have a limited capacity. They are not infinite, and the more chemicals or the more radiation or other carcinogenic agents that that individual is exposed to, you will begin to find that those protective mechanisms no longer protect.

"Now, if you are dealing with a population of many people over long periods of time, it is inconceivable to me that on a population basis, these people will not be exposed to a varying amount of other carcinogens and obviously, we are every day, if our death rate is 16 percent from cancer. Other drugs and chemicals which can influence these various

protective mechanisms, infections which can influence these various protective mechanisms, the intrinsic genetic variability of the population where some people are richly endowed in these and some are not, and this is why I say that as populations, it is very hard to conceive as a threshold, and further, with a 16 percent incidence of cancer deaths, I think it is clear we have all exceeded those thresholds". (Rall, Tr. 483–484)

Several witnesses expressed the opinion that, if there is a threshold mechanism for carcinogenesis, it would probably be determined at the cellular level and that particular values would characterize each individual rather than the entire human population. Thresholds of this nature would not simplify the regulatory dilemma as was explained in the written submission of Dr. John A. Zapp (Du Pont):

"In the relatively small finite populations studied in the laboratory it is generally possible to find a 'no-observed effect level' (NOEL). But the question remains that in large populations there may be a few individuals who react to lower doses than any individual in the observed population. Hence for regulatory purposes some extrapolation of the risk to very large populations must be considered in attempting to get acceptable dose levels. As an example, that dose might be set at a level which might be expected to affect only one person per million at risk. Various formal schemes have been proposed to make such extrapolation, but have not been widely adopted for regulatory purposes.

"Several things should be observed about these extrapolations: (1) each leads to an unverifiable conclusion; (2) each takes us far from the observed data base into the unknown; (3) each is dependent on subjective assumptions about how the dose-effect curve goes in the unobservable region; and (4) none leads to a guaranteed safe finite dose for every individual in the population." (Zapp, S. 20)

Summarizing this evidence, it is possible to postulate that each individual human has a tolerance level for a given substance, but as to any given population, no threshold would necessarily be anticipated. OSHA is, of course, required to protect populations of workers against the effects of carcinogens. For this reason, evidence presented in the Record suggesting the existence of thresholds at the cellular or individual level was not particularly helpful, except where it was explicitly related to the prediction of population thresholds.

Perhaps because of the strong association of the two concepts in toxicology, there was a tendency by some witnesses to confuse the existence of a threshold with that of a dose/response relationship and to assume that, without a threshold, a dose/response curve would not be logical. For example:

"What are the unique chemical and physical properties of carcinogenic agents? What is unusual in their anatomic and metabolic fate that could be expected to isolate them from 'dose response' and 'threshold?' Most important, what might be the characteristics of the development and natural history of the group of diseases we call cancer, which, when viewed as a continuum, might erroneously generate the position that cancer originates in a non-threshold event and progresses in a nondose-response manner?" (Dr. Paul Kotin, Johns-Manville, S. 16)

* * * * *

"There is abundant experimental testimony supporting the view that the effect of carcinogens, like that of other biologically active substances, is dose related and that there are levels of intake below which no effect can be observed." (Dr. Paul Woolrich, AIHA, S.6)

* * * * *

"In the case of certain exogenous carcinogenic factors, epidemiological studies suggest the existence of a threshold. Cigarette smoking, for example, is well known to cause human cancer in a dose-related fashion." (Truhaut, 1977, p. 33–34; Exhibit 24 to Scala Statement)

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"While it recognizes dose-response relationships in the case of 'known' carcinogens, it questions the existence of thresholds and chooses to treat any substance shown to be carcinogenic in animals as having no 'safe' or 'no-effect' levels." (Dr. Bernard Oser, AIHC, S.19)

The assumption implicit in these quoted passages, that a dose-response relationship is synonymous with the existence of a threshold, is not justified. It is possible to envisage dose-response relationships for carcinogens without thresholds, and indeed many such relationships were discussed by witnesses at the hearing (e.g. by Dr. Hoel (NIEHS), Mr. Peto (Oxford Univ), Dr. Rall (Director, NIEHS), and Dr. Schneiderman (NCI)). Drs. Gehring and Blau discussed this confusion in their article quoted above:

"For chemical carcinogenesis, dose-response is not a universally accepted concept. However, its lack of universal acceptance is likely the result of the erroneous assumption that the dose-response and threshold concepts are inextricably associated. Chemical carcinogens, regardless of chemical composition, produce a greater incidence of cancer when administered in large doses than in smaller doses and a dose-response curve does exist (Weisburger, 1975). It may be argued that for some chemicals the response is related linearly to dose rather than to the logarithm of the dose. However, this deviation, if true, does not preclude the establishment of a dose-response relationship. Furthermore, such a deviation does not alter, whatsoever, application of the dose-dependency concepts to the hazard assessment of chemicals, as will be presented later." (Gehring and Blau, 1977, p. 165; Exhibit 9 to Hoel Statement)

An article by Dr. Irving Selikoff (Mt. Sinai School of Medicine), introduced into the Record by Du Pont, also made this clear:

"3. Threshold levels for carcinogenic agents—The existence of dose-disease response relationships is not a contradiction of the concept that thresholds do not exist for the occurrence of cancer following exposure to carcinogenic agents. The fact that it may be very difficult to obtain definitive information on the incidence of cancer at very low levels of exposure provides a background for our current uncertainty in this area." (Selikoff, 1975, p. 91; Attachment I to Du Pont Post-hearing Comment).

When questioned at the hearings, Dr. Paul Kotin (Johns-Manville) firmly stated that a dose response relationship did not necessarily imply a threshold (Kotin, Tr. 4928).

Several witnesses argued that the fact that some exposed individuals do not develop cancer implies a common threshold for all:

"What is important is to recognize that there are exposures possible that will not automatically result in cancer."

* * * * *

"The list is potentially endless, and encompasses virtually every facet of life for all of us. Why, then, do we not all die from cancer? Again, the answer must be that nature has devised biological thresholds that function to protect us from casual exposure to potential carcinogens." (Organization Resources Counselors, S. 36, 43)

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"The no-safe-level hypothesis is denied readily by the populations who have been at long-term risk in an acceptable risk environment to the many toxic materials with which we are surrounded. The no-safe-level hypothesis ignores the capacity of the human organisms not only to accommodate to finite low levels of toxic materials, but also to make beneficial use of them." (Dr. Blaine Mays (Chemetron), Tr. 8189)

However, the wide variability in susceptibility to cancer within a population was pointed out by many witnesses: Dr. Harold Stewart (NIH), S. 4–5; Dr. William Lijinsky (NCI), Tr. 1017; Dr. Donald Kennedy (Commissioner, FDA), Tr. 578–579; Dr. Umberto Saffiotti (NCI), Tr. 950, Dr. Curtis Harris (NCI), Tr. 2017; and Dr. David Kaufman (Univ. of N. Carolina), Tr. 2200.

Another paper cited by several witnesses argued vigorously against the importance of stochastic processes in carcinogenesis:

"Although this approach [MTD bioassay] may be acceptable for screening chemicals for further evaluation, translation of the data to predict the hazard of low-level exposure is

presumptuous guesswork at best. The presumptuous guesswork has been sophisticated by the statistician who has applied his stochastic, statistical processes, and "stochastic" (which is defined as guesswork) is emphasized. Not considered in making such statistical extrapolations is the fact that the fate of many chemicals changes as the magnitude of the dose." (Gehring et al., 1977, p. 187, Reference to Bates Statement).

Dr. Marvin Schneiderman (NCI) and his co-workers presented a more sophisticated view of this issue:

"The importance of Falk's work on threshold is to remind us of the complexity of the carcinogenic process and, although Falk doesn't say it directly, of the stochastic or probabilistic nature of the process. He reminds us that we must not lose sight of the possibilities of anticarcinogens, or chemo-prevention, but this involves an entirely different set of concepts and no generalization seems possible at this time. While Falk gives arguments about numbers of molecules necessary, inactivation, and reaction with cellular constituents other than DNA they all have force. What he neglects to tell us is that these reactions are not likely to be perfect, complete. He doesn't discuss whether it is likely that many paths lead to the (possible) same somatic mutation that is one stage in the development of cancer. Incomplete deactivation and incomplete repair or "unscheduled" repair remain very likely and being likely, and being contributors to one or more stages of carcinogenesis, we should see not threshold, but rather lowered real dose and thus lower, but still non-zero probability of cancer." (Schneiderman et al. 1978, pp. 12–13; Appendix D to Schneiderman Post-hearing Comment)

Thus, rather than being "guesswork", a stochastic view of carcinogenesis takes into account that the process is not understood in complete detail and that its causal components extend to the molecular level which will probably never be entirely predictable.

d. Specific Points at Issue in the Record

After clarification of these areas of confusion, the principal scientific issues raised during the proceeding were the following:

1. Are there features of the process of chemical carcinogenesis which distinguish it from other toxicological processes and would invalidate the automatic extension of the principle of thresholds?
2. Are there protective mechanisms that would eliminate the possibility of carcinogenic effects at low doses?
3. Is it logical to assume that there must be thresholds for "bionutrients"?
4. Have thresholds ever been observed for specific carcinogens in laboratory animals or in humans?
5. Is there a consistent relationship between dose and latent period that would result in a practical threshold at low doses?
6. Would the interaction between carcinogens invalidate the concept of a threshold?
7. Are all individuals equally susceptible to the action of a carcinogen?

1. Distinctive features of carcinogenesis.

Several witnesses expressed the opinion that carcinogenesis should be similar to other toxicological processes in various respects, including the existence of thresholds. For example, Dr. Paul Kotin (Johns-Manville) made the following statement:

"1. *A dose must exist below which a carcinogen is ineffective.*

"Chemical carcinogens of every known category, chemical composition, and steric configuration produce more cancers when administered in large doses than smaller ones, and a dose response curve can be demonstrated for graduated doses (references omitted)

"Carcinogens are like all biologically active substances; they owe their effect to the manner in which they react with the chemical constituents of living organisms. For active substances in general, the greater the extent of reaction, the greater the magnitude of effect. Moreover, the response of a biological system (both experimental animal and human) to a physiologically active agent is proportional, over some range of concentrations, to the concentration of the active agent within the system.

"In the scientific community there are investigators who maintain that the evaluation of the effects and response of a carcinogenic substance should be different from the evaluation of the effects and responses of toxic chemical substances that are not carcinogens. Disregarding established principles of dose response and biological thresholds, they believe that the effect of a carcinogen is all or none, that a single molecule is sufficient of itself to be the ultimate agent of harm, whereas they believe a biological system can tolerate certain concentrations of a noncarcinogenic toxic chemical without any demonstrable adverse effect. There are convincing theoretical arguments as well as data to show that a dose must exist below which a carcinogen is ineffective." (Kotin, S. 11–12)

Dr. Harry Skalsky (Reynolds Aluminum Co.) stated:

"Thresholds exist for every biological phenomenon. OSHA, as a matter of policy, and FDA, as required by law, do not recognize a minimum level of a carcinogen. However, recent advances in cellular biology indicate that this position should be modified." (Skalsky, Tr. 7588)

In their article "Mechanisms of Carcinogenesis: Dose Response", Gehring and Blau delineated the stages at which a threshold might come into effect:

"(1) Chemical carcinogenesis is a multistage process involving:

(a) Exposure, absorption, distribution, activation, deactivation, and elimination of the chemical per se or products formed from it.

(b) Interaction with critical receptor sites leading to molecularly transmittable products.

(c) Survival and proliferation of transformed cells to clinical cancer.

"Interference with any of these processes may constitute a threshold. For example, there is a plethora of data showing that promoters, which in themselves cannot initiate cancer, can enhance greatly the incidence of cancer induced by administration of an initiator. Also, the damaged receptor site may undergo repair." (Gehring and Blau, 1977, p. 165; Exhibit 9 to Hoel statement.)

The late Dr. Hardin B. Jones (Univ. of Calif.), however, distinguished in his submission between toxicants and carcinogens in terms of whether or not they have a threshold:

"In carcinogenesis, the dose response relationships follow closely to a direct proportion between degree of exposure and incidence of neoplasms. Such quantitative relationships indicate a constant risk of neoplastic change per unit exposure to the carcinogen, and there are many carefully done examples showing this to be the rule. Biology has advanced in the theory of understanding of the process of carcinogenesis and we believe that this constancy of risk reveals an underlying molecular process. Dilution does not affect the characteristics of this molecular process which stays constant per unit of dose over a much wider range than is the case with forces causing physiologic change."

"Toxic substances induce physiological disturbances, since the degree of disturbance depends upon the extent physiological controls are overloaded. Toxicant effects subside disproportionately rapidly on lowering dosages; viewed the other way, they begin from a threshold level and build up gaining in degree of effect per unit dose as dose increases. My analysis shows that the appearance of the liver "neoplasms" with exposure to chloroform, chlordane or heptachlor fits the dose response dynamics of toxicant and not of a carcinogen."

* * * * *

"The difference between toxicants and carcinogens is that, with decreasing dose, toxicants reach a no-effect level, a threshold, and as the threshold is approached, the toxic effects greatly subside. In contrast, true carcinogens continue to exert influence, as dose decreases, and the tumor risk appears constant, per unit of carcinogen, over the detected range of cancers. Yet through animal bioassays at very high doses, toxicants may be implicated in the causation of cancer. Examples of such toxicants for which thresholds can be established are chloroform, carbon tetrachloride, chlordane and heptachlor." (Jones, S. 4, 19–20)

Dr. Arthur Upton (Director, NCI) provided an explanation of the differences between carcinogenesis and other toxicological processes:

". . . experience teaches us that the kind of toxicity that results in acute renal shutdown, that results in respiratory failure,

cardiac arrest, acute hematologic insufficiency, generally involves a measure of tissue insult that does in fact to all practical intents and purposes represent a threshold; whereas with other kinds of effects, we may be dealing with subtle injury to perhaps only a single cell in the body: The induction of a mutation in a germ cell; induction of a carcinogenic change in one of the body cells.

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". . . I only have to damage perhaps one cell in the bone marrow to give myself leukemia, and that is the problem. That is the great difference between this threshold phenomenon in toxicology and the non-threshold phenomenon.

"We have to be much more careful about the non-threshold category because that type of damage, for what we know about it, is permanent. It is not reversible." (Upton, Tr. 343–345)

Dr. Upton enunciated four principles that apply to radiation carcinogenesis, and proposed that on the basis of present knowledge it would be prudent to apply these principles to chemical carcinogens. The first two of these principles were:

"1. Any exposure to ionizing radiation is considered to pose some risk of increased cancer incidence.

"2. At low exposure, the excess risk is considered likely to be proportional to the increase in exposure (relative to background)." (Upton, S. 6–7)

Another specialist in radiation carcinogenesis, Dr. Richard Wilson (Harvard Univ.), agreed with the application of these principles to chemical carcinogenesis (Wilson, Tr. 3421), as did Dr. Bo Holmberg (Swedish NBOSH) (Holmberg, S. 14).

In a 1975 publication by Dr. Upton, observations on dose-response relationships for radiation carcinogenesis were summarized as follows:

"The dose-incidence relation in experimental animals is generally curvilinear, with the following features: (a) in the high dose region, the incidence tends to reach a plateau or to decline with increasing dose, presumably because of excessive injury (Upton, 1967; United Nations, 1972); (b) in the intermediate dose region, the incidence tends to rise more steeply with increasing dose than at lower or higher dose levels; (c) with decreasing dose and dose rate, the curve tends to become shallower, at least in the case of low-LET radiation.

From the foregoing, the cancer biologist is tempted to infer that at low dose levels (1) "initiating" effects of radiation predominate, which are to some extent reversible in incipient stages; (2) these effects may be magnified by other types of effects ("enhancing," "promoting" etc.) at intermediate dose levels; and (3) both types of carcinogenic effect fail to be expressed fully at high dose levels, because of side-effects or excessive injury." (Upton, 1975, p. 397)

This passage was erroneously quoted at (Tr. 4884) as though it supported the concept of a "no effect level", although in fact it stands for exactly the opposite position, as reflected in Dr. Upton's direct statement.

Dr. Upton also quoted a 1960 Report of the Federal Radiation Council:

"There is a particular uncertainty with respect to the biological effects at very low doses and dose rates. It is not prudent, therefore, to assume that there is a level of radiation exposure below which there is an absolute certainty that no effect may occur.

"This consideration, in addition to the adoption of the conservative hypothesis of a linear relation between biological effect and the amount of dose, determines our basic approach to the formulation of radiation protection guides." (Upton, 1975, p. 399)

To paraphrase the WHO Technical Report 546 (pp. 9–10) quoted in the proposal: Carcinogenesis, whereby one event can cause irreversible damage in a single cell which can be perpetuated by self-replication like a somatic cell mutation and produce an observable effect only after long latency, is qualitatively very different from the acute or even chronic non-carcinogenic effects of toxic chemicals. Carcinogenesis now appears to be a multi-causal, multi-stage disease process which involves the interaction of a multitude of inherited susceptibility factors and environmental risks.

Dr. Schneiderman (NCI) and his colleagues discussed some of the unique properties of carcinogens:

"Is cancer different then from other ills the flesh is heir to? (This cliche does not necessarily imply a genetic mechanism). There is evidence that it is different. Dinman in advancing his theory of the "minimum number of molecules" required for damage did not include cancer among the diseases that his argument would apply to. First, cancer appears often to be a disease of DNA damage or mis-repair, or incomplete repair and there is evidence that large numbers of molecules of an offending agent are not needed to cause DNA damage. Second, cancer is a progressive process. Once the last stage is started, the cells appear to develop an existence of their own, growing out of bounds as it were. The initiating agent doesn't need to be present any longer once the process has started on its way (although a "promoter" may need to be around for a long time to produce high risks). Third, many agents seem to lead to the same cancer. This implies that unlike bacterial diseases where one agent leads to one disease, we must not consider each agent in isolation, but we need to put the doses of these same end result materials together additively (at least). If n materials lead to the same event and each is at an effective dose of d_i, and each one of these below its own separate threshold, assuming there was one, we would have to be concerned whether the sum of the d_i would be below the organism's personal threshold. Thus, on a theoretical basis, if the same cancer can be brought about by several agents, being exposed to each of these agents below its own individual threshold could still lead to the sum of the exposures exceeding the threshold for the organism." (Schneiderman et al., 1978, pp. 2–3; Appendix D to Schneiderman Post-hearing comments)

Dr. Robert Squire (Johns Hopkins Univ.) also expanded upon the unique aspects of carcinogenesis in his prepared statement:

"It is well established that carcinogenesis, like other forms of toxicity, is dose-dependent, and carcinogenic risk often correlates with levels and duration of exposure to carcinogens (Druckrey 1967). In contrast to other forms of toxicity, however, there may be a cumulative effect of exposure to a carcinogen because of the irreversible nature of the carcinogenic toxicity. This has been demonstrated in animal studies and by the increased incidence of respiratory cancer in chloromethyl methyl ether workers as related to cumulative exposure. Nelson (1976, p. 87) stated, "Again, lung cancer occurrence follows in an orderly way the cumulative time-weighted exposure."

* * * * *

"It is probably true that all substances are toxic at some level and that most are safe at another, since many metabolic, pharmacokinetic, and detoxification or repair processes are dose-dependent.

"Not all substances, however, are carcinogenic, including many that exhibit other types of toxicity and can cause death. In the current NCI carcinogenesis bioassays (reports in progress), over one-half of the substances tested showed no carcinogenic effects, although most were to some extent toxic at the levels tested. These results are particularly revealing, since the chemicals were selected for testing because some concern for their carcinogenic potential existed. Carcinogenicity is in fact a specific type of toxicity, resulting in a persistent and self-perpetuating alteration of cells, apparently through the interaction of the ultimate carcinogen and cellular genetic material or other cellular macromolecules that control cellular differentiation (Miller 1977). It is perhaps identical to somatic mutation, a type of genetic toxicity, but it is to be distinquished from most other types of toxicity, which do not result in heritable cell alterations. The mechanisms of carcinogenicity are unknown, but the phenotypic expression of the carcinogenic process is clearly different from that of non-neoplastic toxicity.

"Thus, I believe that we are compelled to consider carcinogenesis a specific and perhaps unique toxic manifestation. We should not, in my view, regulate carcinogens as we do many other toxic substances." (Squire, S.5, 7–8)

Dr. Richard Griesemer (NCI) stated similarly:

"The assumption that the "principles of toxicology" apply to carcinogenesis has not been proved. In particular, the evidence that exposure of cells to very small amounts of

carcinogens results in irreversible changes that can be shown to be the beginning of the carcinogenic process indicates that caution should be used in attempting to predict threshold levels until more data are obtained." (Griesemer, S. 7)

Dr. Curtis Harris (NCI) testified also about the irreversibility of early stages in cancer induced by cigarette smoke:

"There is some evidence that the histological appearance of the metaplasia, the amount of metaplasia, the number of foci decrease in number and in extent. There is no evidence that they go away completely, and there is no evidence that the carcinogenic process is reversible. . . ."

"What happens. . . is that the risk plateaus off, but it is still a much higher risk than someone who does not smoke, and I think that is—so far, as we know, it is an irreversible process." (Harris, Tr. 2023–2024)

Dr. Hoel, Mr. Peto, and their colleagues summarized evidence that cancers often originate from single cells:

"Single-Cell Origin. If individual cancers arise from an original, single, "transformed" cell, then the statistical nature of the carcinogenic dose response will be governed by the extreme tail of the "transformation" response distribution. The effect of this is to make virtually any process of discrete events approximately linear at low dose. Two primary observations indicate the single-cell origin of cancers. In women who are heterozygous for electrophoretic variants of X-linked glucose-6-phosphate dehydrogenase, cancers are uniformly of one phenotype or the other (6), whereas a comparable amount of normal tissue is composed of a mixture of cells of the 2 phenotypic classes. Further evidence for the single-cell origin of cancers comes from experimental efforts in which "transformed" cells are transplanted into whole animals. Although there is much controversy associated with various aspects of this line of research, it seems that the ability of a single cell to give rise to a cancer is well demonstrated (7). Thus, 2 lines of evidence indicate that cancer can be most reasonably assumed to arise from events associated with or occurring inside single cells. (6)" (Crump et al., p. 2977 (citing Fiaklow, 1974 and Gartler, 1974). (Annex C to Peto Statement).

These points were discussed more fully in the Introduction (see Chapter III. A. *The Nature of the Disease*). The consensus of the scientific witnesses was that carcinogenesis is a distinctive process which differs from other toxicological processes in several key features. There is, therefore, no sound reason to assume that it must necessarily resemble other processes in displaying a threshold. Indeed, there are substantial empiricial and theoretical reasons why it should not.

(2.) Protective mechanisms.

One phenomenon which was proposed as a mechanism that might lead to a threshold in carcinogenesis is immuno-surveillance:

"There is a substantial and growing body of evidence that carcinogenesis is subject to immunosurveillance, particularly cell-mediated immunity (Roe and Tucker, 1974; Weisburger, 1975)." (Gehring and Blau, 1977, p. 166; Exhibit 9 to Hoel Statement)

However, the significance of this mechanism was questioned by Dr. Curtis Harris (NCI):

"Q. What I am asking you is if you had evidence that immunosuppression led to an increased incidence of cancer—

"A. Well, you are talking about something that is very hypothetical and you just said that you have no evidence—there was a theory, and I guess it is still a theory, that there is such a thing as immunological surveillance, and that has become a bit passe now.

"There is an association, that is a fair statement, but there is an association between the risk of cancer and a lot of exogenous factors . . . Most of the increased risk happens to be in a couple of very rare kinds of tumors, such as lymphomas, and it is not clear whether or not the immunosuppression per se was the cause of it or the antigenic stimulus of the kidneys, the foreign kidneys, from another individual that we put into the patient, or a combination of the two. The mechanism of that, frankly, is not known." (Harris, Tr. 2040)

Another mechanism cited by a number of witnesses that might hypothetically lead to a threshold effect at low doses is DNA repair. Several witnesses cited the example of *xeroderma pigmentosum* to illustrate the importance of DNA repair. Persons suffering from *xeroderma pigmentosum* are characterized by an impaired ability to repair DNA and are much more susceptible to skin cancer after exposure to ultra-violet light than normal persons, e.g.:

". . . there is a tendency to denigrate repairs, but let me give you an example of where repair represents the difference between the manifestation of a disease or its non-occurence, and that is cancer in patients with xeroderma pigmentosa.

"It is the absence of one repair mechanism that is the fulcrum which determines the occurrence or non-occurrence of cancer." (Kotin, Tr. 4893)

However, the logic of this statement and its application to the threshold concept are not clear. Skin cancer is frequent in persons who do not suffer from *xeroderma pigmentosum*: hence the reference to "non-occurrence of cancer" was incorrect.

Dr. Umberto Saffiotti (NCI) discussed this repair mechanism and the individual susceptibility it is subject to at length during his oral testimony:

"We know that xeroderma pigmentosum patients—these are patients with a special genetic disorder that makes them extraordinarily susceptible to the induction of skin cancer by agents such as sunlight—we know that these patients with this particularly high genetic susceptibility would develop literally hundreds sometimes or certainly a large number of skin cancers, essentially by the age of 20 or something like that.

"And we know that if we have people of a somewhat lower level of susceptibility but still very high, which I characterize by certain genetic features in their skin complexion, we know that those are particularly high-risk individuals. Now, if we have certain occupations that involve high-level exposure to actinic radiation, to sunlight, such as certain agricultural or marine activities and others, or certain activities in exposure to sunlight at high altitudes, we know from epidemiologic studies that some of these people are indeed at a very high risk for skin cancer. We also know that if they are protected from sunlight this skin cancer would not appear. There is a recent case report on two patients diagnosed with this genetic condition, xeroderma pigmentosum, at birth because of their genetic background who have been raised in complete protection from sunlight, yet with living a fully active life, having outdoor exercise after sunset and such provisions, they are now 18 or something like that. They were reported when they were 18 years old, and they have not had a single skin tumor, which is extremely different from what you would expect from such very high-risk people if they had had exposure to this agent.

"Now, what I am really driving at is that even the very high-risk people can be effectively protected by removing the exposure, and that one should always worry about high-risk individuals in the population. For those cases where we do not know what the high-risk markers are, then obviously we take a prudent attitude of cutting down all the exposures. The question is posed whether we should select employment characteristics or exposures and so on for those people. I think that without going into the legal and labor negotiation aspects of that problem, certainly all the information should be made available to such people that would indicate to them, with documentation, what are the high risks that they could take and those they would be particularly affected by. What I would say is that if I would advise, as a scientist, an employer who has to have a crew of people working at high altitudes in sunlight, I would make these points known to them so that the workers and their unions would be fully informed of this particular aspect. Beyond that, I know there are policy issues that I am really not in a position to sort out. They are delicate problems of freedom of employment and all that.

"But what I want to stress in this context is that even for those high-risk people, there can be protective mechanisms that would prevent their exposure to this agent and allow them to work even in what other people consider an exposure case, protecting them from their exposure. So I think you do the best you can under both circumstances." (Saffiotti, Tr. 986–908)

A detailed description of DNA repair mechanisms was provided by Dr. Ronald W. Hart (Ohio State Univ.):

"It thus appears a reasonable assumption that excision or prereplication repair plays a primary role in the modulation of the carcinogenic potential of a number of chemical and physical carcinogens and thus should be considered when evaluating their potential hazard. This may be especially the case since it is a reasonable expectation that the capacity of a cell to repair DNA damage may determine its threshold level for such physiological endpoints as cytotoxicity, mutagenicity, and potential carcinogencity. For example, XP fibroblast cell cultures from patients of complementation Group A (the most excision repair defective class of XP patients) have a lower threshold level for cytotoxicity and mutagenicity (for many physical and chemical carcinogens) than do fibroblast cell cultures derived from normal individuals.

"Strand Break Repair

"A second general form of DNA repair is strand break repair. Strand break repair is generally measured by following the rejoining of single-or double-stranded DNA on, respectively, an alkaline or neutral sucrose gradient subsequent to exposure of cells to either X-rays or chemical alkylating agents. Breaks in DNA may arise from: a) alkali-labile apurinic sites in DNA, b) alkali-labile phosphotriester groups in alkylating DNA, c) cellular metabolism, and d) the action of excision repair enzymes. Regardless of the nature of the factor inducing strand breaks in cellular DNA treated with either X-ray, alkylating agents or 4NQO, with the possible exception of the latter, there is little data suggesting correlation *in vitro* between strand break repair and carcinogenesis.

"Postreplication Repair

"Postreplication repair is a process in which DNA newly synthesized from a defective or damaged template is repaired. This concept was derived from the observation that newly synthesized DNA in UV-irradiated cells is initially of lower molecular weight than in unirradiated cells. The gradual increase in molecular weight on subsequent incubation of UV-irradiated cell cultures has been interpreted as the repair of gaps formed in the newly synthesized DNA opposite the UV-induced DNA lesions. Obviously, this system would be important only in cells actively synthesizing DNA and in cells that were unable to excise all lesions from their DNA prior to the onset of DNA synthesis.

"In bacterial systems, it is now fairly certain that mutations may be induced by either mispairing of the DNA bases during DNA replication or by misrepair during postreplication repair. Both misreplication and misrepair can be induced by DNA damage entering DNA replication. Other causes for the induction of misreplication have been covered in an elegant review by Drake and Baltz and will not be covered here. While misrepair (presumably postreplication repair, since prereplication repair is assumed to be error-free) has been directly related to mutagenesis in bacterial systems, the evidence for either postreplication repair (error-free or error-prone) or its mutagenic nature is, at best, only indirect in mammalian systems. This evidence includes: a) the existence of a variant form of xeroderma pigmentosum which is normal for excision or prereplication repair, but is abnormal with regard to the rate at which newly synthesized (lower molecular weight) DNA in UV-irradiated cells increases in size on subsequent incubation (these studies presumably indicate an error in postreplication repair); b) the observation that xeroderma pigmentosum cells derived by XP variant individuals have a higher than expected mutation frequency following exposure to certain carcinogens such as UV-light, polcycylic aromatic hydrocarbons, and acetoxyacetyl-aminofluorene; and c) the observation that caffeine, a known blocker of error-free postreplication repair in certain bacterial systems, enhances under selected conditions the number of ouabain-resistant mutants in the Chinese hamster cell line V-79. Thus, while it is tempting to suggest that mammalian cell mutagenesis and carcinogenesis may be partly due to an error-prone postreplication repair system occurring in mammalian cells, as it apparently does in bacterial cell systems, there is at this time insufficient evidence to draw such a conclusion.

"From the evidence presented in Section 2 above, it is apparent that various forms of DNA repair systems operate in mammalian cells and, further, that these systems operate to remove DNA damage induced by both physical and chemical agents. The form of DNA repair most closely associated with modulation of the cytotoxic, mutagenic, and carcinogenic action of physical and chemical carcinogens appears to be excision or prereplication repair. While other forms of DNA repair may also modify the cytotoxic, mutagenic, and carcinogenic action of environmental agents, the lack of scientific data makes it difficult to draw such a conclusion. It is, however, a reasonable assumption that at least excision repair is a major modulator of the carcinogenic and mutagenic potential of many but not all carcinogens." (Hart, S. 20–23)

Dr. Hart went on to summarize his comments as follows:

"35. The presently available evidence suggests that:

(a) DNA is the primary target for most but not all physical and chemical carcinogens;

(b) For many chemical carcinogens metabolic activation is required to produce the carcinogenic form of the agent;

(c) DNA repair (of at least the excision form) appears to modulate the cytotoxic, mutagenic and carcinogenic potential of physically or chemically induced DNA damage;

(d) Correctly repaired DNA damage is assumed to have no deleterious biological effect;

(e) Unrepaired DNA damage, entering DNA replication, is believed to produce mutations by either misreplication or misrepair;

(f) For many, but not all carcinogens, mutagenesis appears to correlate well with carcinogenesis.

"36. It is thus a reasonable assumption that species differences in either or both the ability to metabolically activate chemical carcinogens or repair carcinogen-induced DNA damage would relate to the carcinogenic potential of many of these agents. The presently available evidence on species differences with regard to these two factors is meager, but suggests that:

(a) Fibroblasts derived from longer-lived species (e.g. humans) are less able to metabolically activate the polycyclic aromatic hydrocarbons than those derived from shorter-lived species (e.g. mice).

(b) Fibroblasts derived from longer-lived species (e.g. humans) are better able to excise UV-induced DNA damage than those derived from shorter-lived species (e.g. mice).

"37. If further examination shows that humans cells have either a lesser or greater ability to repair various forms of DNA damage than cells from rodent species and/or that human cells have either a greater or lesser ability to metabolically activate various chemical agents to their carcinogenic forms than rodent cells, then either way these factors should be taken into account when setting threshold levels for occupational exposure to potentially hazardous agents." (Hart, S. 27–28)

Strictly speaking, *any* failure in repair leaves the possibility of initiation of the carcinogenic process and so precludes the existence of a threshold. Dr. Hart in his exhibit "The Role of DNA Repair in Aging" indicated that the repair process is not 100% reliable:

"The majority of the genetic information in a differentiated cell is normally nontranscribable (Cutler, 1974). Most mammalian systems do not show total repair of DNA damage and the fraction of damage repaired decreases as the amount of insult to DNA increases (Hart and Setlow, 1974). Preferential repair of DNA damage in nonchromatin-bound DNA following UV-irradiation has been demonstrated in human fibroblast cultures in vitro (Wilkins and Hart, 1974). When previously UV-irradiated cells are exposed to a high salt solution and the number of endonuclease-sensitive regions remaining are determined, a significant fraction appear to remain unrepaired in the chromatin-bound regions even several days after UV treatment. Thus, even if the rate of occurrence of random DNA is constant and the fraction of new damage accumulates at a constant rate over the lifespan of an animal, it would be expected that there would occur a preferential increase in the amount of distortion of the DNA helix in the chromatin-bound regions of the DNA.

"At the functional level, unrepaired or incorrectly repaired DNA damage can be reflected in (1) transcription of erroneous mRNA; (2) synthesis of nonfunctional enzymes; (3) cessation of transcription; or (4) gene de-repression (Trosko and Chang, This Volume; Trosko and Hart, 1975). In any system where repair of DNA is incomplete and damage thus accumulates with time, the results of these functional alterations would also be expected to increase. When the amount of damage a system can tolerate is exceeded, system malfunction and death ensue." (Hart, 1976, p. 540–541; Exhibit to AIHC Statement)

The critical issue is whether DNA repair is 100 percent efficient in some or all circumstances. Some witnesses stated that excision repair is 100 percent efficient (Dr. Robert Olson (St. Louis Univ.), Tr. 3332; Dr. James Jandl (Harvard Univ.), S. 19–20), but agreed with Dr. Hart that postreplication repair is not (Jandl, S. 19–20). Dr. David Brusick (AIHC) was equivocal on the issue, stating that "the DNA repair system can eliminate essentially 100% of induced lesions . . .", but without specifying which type of repair was being referred to.

Dr. Arthur Upton (Director, NCI) made the following statement:

"We know of repair mechanisms that operate on the gene, but we know that they do not operate with 100 percent efficiency. So that there is always some residual level of damage that is not repaired.

"We also know that there can be misrepair of damage, and there is some evidence that it is in fact the misrepair, the faulty repair, that eventually leads to cancer." (Upton, Tr. 346)

Dr. Bertram Dinman (Alcoa) went further and expressed the opinion that none of the repair mechanisms could be expected to be 100 percent efficient:

"Q. On page 2 of your statement, the very last paragraph, you have written: "By 1978 it has become apparent that errors in DNA sequences can be corrected by at least three general mechanisms," and you list excision or [pre] replication repair, strand break repair, and post replication repair.

"To the best of your knowledge, are any of these repair mechanisms known to be 100 percent effective?

"A. I do not think there is any biological phenomenon which could be expected to occur 100 percent of the time." (Dinman, Tr. 7028–7029)

OSHA concludes from the testimony cited above that DNA repair is not normally 100 percent efficient, and indeed that it would be unreasonable to expect it to be so. Accordingly our knowledge of DNA repair cannot be used to justify the assumption of population thresholds for carcinogens, either in general or in specific cases. In addition, DNA repair appears to be a general phenomenon and would be expected to be significant in experimental animals as well as exposed humans. Accordingly, its principal significance from the point of view of regulation is for the quantitative rather than the qualitative extrapolation from animals to humans. At present there is insufficient evidence for interspecific comparison of repair efficiency (Hart, S. 23–28; Tr. 3500), but any variations in efficiency would greatly complicate the problem of quantitative interspecific comparisons.

A third protective mechanism cited by many witnesses is the detoxification of carcinogenic metabolites prior to their interaction with DNA or other cellular macromolecules. Some aspects of this mechanism have been discussed above relative to the hypthesis of "metabolic overloading" at high doses. The specific question relevant to threshold is whether detoxification mechanisms can be 100 percent efficient *at low doses.*

Dr. Ralph Freudenthal (Stauffer Chemical Co.) spoke of the possibility of detoxification:

". . . there is a concentration at which detoxification can handle the material in such a way that the reactive metabolites do not get to the critical macromolecules, and therefore you do not get tumorigenicity. So I believe not only in these studies is there a no-effect level. I think there is a real no-effect level." (Stauffer, Tr. 6758)

However, Dr. Curtis Harris (NCI) challenged the idea that it would be completely effective:

"We are looking at conjugation of carcinogens with glutathione, sulfates, glucuronides. But as I mentioned, you cannot equate conjugation with detoxification, in that you cannot assume that the detoxification mechanisms are 100 percent efficient. And there are examples in which a conjugate can be deconjugated, leading to the active form of the carcinogen. . ."

* * * * *

"I said that detoxification mechanisms are not 100 percent efficient, and it is unreasonable to believe that they would be, and that what some people call detoxification, conjugation reactions, can in fact lead to a conjugated product that can, by bacteria, or by normal human cells, be deconjugated, and you are right back where you started again, with the active form of the carcinogen."

* * * * *

"No, I think that there are several ways that you might, in understanding the mechanism, be able to prevent carcinogenesis. One is inhibiting activation, and the other is enhancing deactivation. Now, deactivation does not necessarily correlate with conjugation. It we could find a way of making everyone so that they could 100 percent efficiently get rid of carcinogens, that would be very nice. I think that is an unreasonable hope, though." (Harris, Tr. 1998–1999)

A number of witnesses cited in support of the hypothesis of detoxification at low doses a paper by Dr. Jerome Cornfield (Cornfield, 1977; Hearing Exhibit No. 9). This paper, however, only explored the consequences of a mathematical hypothesis, and did not cite any evidence in support of its basic assumptions. In the Record of this rulemaking, it was shown that Cornfield's model: (a) was applicable only at the cellular level, and not at the organism or population level; (b) would apply only to a single dose exposure; and (c) predicted a threshold only in the improbable circumstances in which deactivation was irreversible and takes place instantaneously, before any of the active metabolites is able to interact with DNA (Dr. Marvin Schneiderman (NCI), S. 28–30; Dr. David Hoel (NIEHS), S. 6; Dr. David Rall (Director, NIEHS), Tr. 395–396, Drs. Gerald Chase and Paul Kotin (Johns-Manville), Tr. 4941–4942). Dr. Marvin Schneiderman (NCI) and his colleagues discussed the Cornfield model in a paper presented to the New York Academy of Sciences Conference "The Scientific Basis for the Public Control of Environmental Health Hazards:"

"Cornfield does not claim that this model demonstrates the existence of threshold but rather that the model is sufficiently permissive to accommodate a threshold. The model has been criticized as being deficient in its biological base in that (a) to get the "hockey stick" requires nearly *instantaneous and complete detoxification* or instantaneous achievement of the subsequent steady state; (b) it seems to be concerned with a *single pulsed* exposure and not lifetime exposure, and (c) it has yet to deal with *variation in detoxifying ability* in an exposed population. Cornfield has withheld his model from current consideration as a practical risk-assessment procedure "because it appears to require quantitative information on metabolic pathways that will often not be available." In fact, he gives no example of a case in which this information is available." (Schneiderman et al., 1978, p. 6; Appendix D to Schneiderman Post-hearing Comment, emphasis added)

In his direct testimony Dr. Schneiderman (NCI) concluded:

"Thus, I would conclude if one assumes instantaneous complete deactivation, one can show a threshold. If it is necessary to have instantaneous, complete deactivation, which is biologically most unlikely, to show threshold, then threshold is also most unreasonable." (Schneiderman, S. 30)

Dr. Schneiderman (NCI) included in his direct testimony a letter addressed to the journal *Science* in which some of these objections were presented. Subsequently, this letter has been published by *Science* together with critical letters by G. McGaughey (Veterans Administration Hospital, Long Beach, CA), K.S. Crump (Louisiana Tech. University), J. Neyman (University of California), E. Scherer and P. Emmelot (Netherlands Cancer Institute) (*Science*, 202: 1105–1107, 1978). In reply, Dr. Cornfield stated:

"An author cannot escape complete responsibility for misinterpretation of his writings, but I nevertheless suggest that *only a misreading of my article could have led to characterizing the model given there as a*

threshold model." (Ibid., p. 1107, emphasis added)

Thus there appears to be no substantial evidence, either empirical or theoretical, in the Record to support the concept of a threshold resulting from low dose detoxification.

Another hypothetical biological mechanism presented to support the concept of a threshold is that early lesions induced by carcinogens regress upon cessation or reduction of exposure. Strictly, this mechanism would result in a threshold duration of exposure rather than a threshold dose, below which no cancer would eventuate. One of the two witnesses who offered documented evidence for such an hypothesis was Dr. Leon Golberg (CIIT):

"One view of the primary changes, such as thyroid hyperplasia, that progress to neoplasia, regards them as precancerous processes. The question then arises: Are such primary changes irreversible, or does lowering or cessation of exposure to the agent that elicited them cause them to disappear? The latter course is observed with antithyroid agents (Jemec, 1977). Evidence also exists that, in the liver, bladder or other organs, what appear to be preneoplastic changes can be reversed in their early stages, depending on dose and duration of exposure (Pitot, 1977; Farber, 1976; Pitot, Barsness, and Kitagawa, 1978; Farber and Solt, 1978; Friedell, Jacobs, Nagy, and Cohen, 1977). The implications of these few observations are potentially momentous. They may not be found to be universally applicable, but they do emphasize that measured caution, and a search for understanding, is more appropriate in the interpretation of scientific observations than insistence upon rigid criteria." (Golberg, S. 6)

Dr. Paul Kotin (Johns-Manville), apparently citing the same sources, testified that he had changed his scientific opinion and now believed in the concept of threshold "on the basis of three almost simultaneous, epoch-making observations in liver carcinogenesis":

". . . within the recent past Dr. Farber has convinced himself, and incidentally, he has convinced me, that he has identified some enzymatic markers which are critical to the carcinogenesis in the liver, and he has used a rat model rather than a mouse model. And Dr. Pitot himself has demonstrated, certain enzymatic pathways and enzymatic production of the pathways enzyme, which he thinks are significant to and involved with the development of malignant neoplasms in the liver. And the same of Peter Emmelot of the Netherlands.

* * * * *

"Several things have happened as a result of their studies. One, both Dr. Pitot and Dr. Farber have observed regression of lesions which were characterized as being on the way toward neoplasia. So I guess the reason for my changing my mind is that until such a time—and again, let me say that these are neoplasms in animals with no genetic selection for high liver cancer—so that the whole question of the hepatoma which was used in the diagnosis of—or in the regulation for carcinogens becomes a moot point, that at least using the liver model one cannot say positively that an increased incidence of these genetically predetermined tumors is sufficient to indict an agent as a carcinogen."

* * * * *

". . . Of course liver tumors in mice and rats can predict or show some correlation with liver cancer in man . . . what I am trying to say is that they predict, but do so within the confines of dose response and exposure to levels which do not result in cancer, and even more dramatically, result in the regression of some of the benign nodules, much the same as skin papillomas regress when you have an inadequate dose of a carcinogenic polycyclic hydrocarbon. (Kotin, Tr. 8740–8744)

In response to questions about whether all the "benign nodules" regress at low doses, however, Dr. Kotin replied:

"I can't say some or all. . . . Whether they all regress or not, I don't know." (Kotin, Tr. 8744)

In fact, two of the scientists responsible for these "epoch-making observations" presented testimony in these hearings, and neither cited his own work as supporting the hypothesis of a threshold. Papers by Dr. Pitot and Dr. Farber were introduced into the Record (Pitot, 1977, Hearing Exhibit 181, no. 1; Farber 1973, 1978, Appendices to Farber Statement; Farber *et al.* 1977, Hearing Exhibit 181, no. 2). These papers do not support the issue of thresholds. In fact, Dr. Pitot made the following comments in his prepared statements:

* * * * *

"Although it is true that we can not specify the precise level at which possible hazard to an individual becomes zero, it must also be recognized that living is not a "no-risk" situation.

* * * * *

"Although, as emphasized in the OSHA document, it is not possible to establish a threshold for a chemical carcinogen or even the shape of the dose-response curve at low levels of exposure, many data show that the incidence of tumors decreases markedly as the dose of a carcinogen is decreased." (Pitot, S. 2–3.) (Emphasis supplied.)

And Dr. Emmanual Farber (Univ. of Toronto) commented on Dr. Kotin's interpretation of his work as follows:

"As he correctly pointed out, early preneoplastic liver lesions do regress unless the environment is appropriate for continued stimulation of the initiated cells (promotion). However, we also pointed out that the induction of initiated cells was an irreversible phenomenon. As in the skin, these early lesions were found to persist for long periods (up to 44 weeks) and could be stimulated to proliferate at will by creating the appropriate environment for selection.

"Using our new assay for initiation, we have not found a dose of diethylnitrosamine that does not initiate if accompanied by cell death plus regeneration or better a round of cell replication. Thus, *we cannot be certain that a threshold actually exists for initiation of carcinogenesis. This is particularly so, given the well known variation in susceptibility to carcinogens of animals of different genetic background.*

"Judging by our own work and a knowledge of the published literature, and given the wide variation in susceptibility with genetic diversity, I cannot convince myself that a threshold has ever been clearly demonstrated for initiation of the carcinogenic process." (Farber, Post-hearing Comment, p. 1) (Emphasis supplied)

Finally, Dr. Emmelot, in his response with Dr. E. Scherer to Dr. Cornfield (*Science,* 202: 1978, 1107) pointed out that neither Dr. Cornfield's data nor Dr. Gehring's are consistent with Dr. Cornfield's model. Thus it appears that Drs. Kotin and Golberg were in error in citing the works of Drs. Pitot, Farber and Emmelot in support of the threshold hypothesis.

3. Do "bionutrients" necessarily display thresholds?

A number of witnesses proposed the hypothesis that because certain chemicals ("bionutrients"), which appear to be essential at low doses for the existence of human life, are carcinogenic at high doses in experimental animals, these substances must therefore necessarily have thresholds. This hypothesis is apparently based upon an assumption that "Nature wouldn't do it to us." See, e.g.: Dr. Robert Olson (St. Louis Univ.); Dr. James Jandl (Harvard Univ.); Dr. Bernard Oser (AIHC); Dr. Ronald Hart (Ohio State Univ.); Dr. George Claus (AIHC); Dr. Elwood Blanchard (DuPont); Dr. Leonard Goldwater (AIHC); Dr. John Thorpe (API); Dr. Arthur Furst (Univ. of San Francisco); Dr. Ralph Freudenthal (Stauffer Chemical Co.); Dr. Gary ter Haar (Ethyl Corp.); Dr. Paul Gross (IHF); and Dr. Adrianne Rogers (MIT). Dr. Paul Kotin (Johns-Manville) alluded to this issue in his written submission:

"There are two instances of biological circumstances which unequivocally dramatize the concept of a threshold level of carcinogenic effect. The first relates to the carcinogenicity of certain steroid hormones. Estrogens and androgens are carcinogenic for experimental species, and in the case of estrogens, the occurrence of disease in humans has been documented (23). In the case of the synthetic estrogen stilbestrol and the naturally occurring estrone, cancer has been observed only after the administration of large doses of these agents. Estrogenic hormones are ever-present at *subthreshold* levels in the earth's population.

"The second instance relates to the universal occurrence of certain trace metals, such as nickel and chromium, in the bodies of man (24, 25). In both animals and man these elements have been shown to be carcinogenic at high dose levels. Their physiologic presence, however, is unaccompanied by any demonstrable abnormalities." (Kotin, S. 15)

Other substances cited in this context were tryptophane, Vitamin D, cobalt, selenium, indole, calcium, lactose and maltose.

A number of witnesses contested this hypothesis. Dr. Richard Bates (NIEHS; FDA) discussed the hypothesis as follows:

"On the threshold question, the assumption is often made that since hormones are natural chemicals of the human body, there are levels that are noncarcinogenic and a small incremental exposure over natural levels will have no significant effect. This overlooks the fact that a substantial proportion of human cancers occur in organs under the control of hormones even among individuals who have never received synthetic hormonal chemicals. Thus, "normal" levels of exposure do appear to be related to the development of cancer in some people. A small increase in those levels may have a small impact on the total cancer incidence, but is not necessarily negligible. The problem with the second question is illustrated by the drug, diethylstilbestrol. This drug is carcinogenic in experimental animals (32) and has been shown to cause cancer of the vagina in the offspring of some women who were treated with it during pregnancy (33). It almost certainly can induce cancer through the same mechanism as natural estrogens, but it also has a chemical structure that some have suggested might be capable of being activated to a chemical that can bind to DNA (34), and therefore may act through other mechanisms of carcinogenesis as well." (Bates, S. 17–18)

Dr. Upton (Director, NCI) agreed with this position:

"I do not see that the existence of evidence for essentiality of a material as a trace nutrient is incompatible with the concept that that same material may be carcinogenic in trace amounts. So I don't think that kind of evidence in any way contradicts the notion that there may be in fact no non-carcinogenic or safe level in the cancer risk sense." (Upton, Tr. 272)

And in speaking of sunlight as another example, he remarked:

". . . conceivably in any amount [it] is both deleterious, and in appropriate amounts, useful. There is no reason why it shouldn't be both deleterious and useful a priori." (Upton, Tr. 348)

Dr. Robert Squire (Johns Hopkins Univ.) submitted a post-hearing statement concerned with the question of bionutrients. At the outset, Dr. Squire stated:

"Several witnesses proposed that no-effect levels or 'thresholds' of carcinogens are demonstrated by the fact that some essential bionutrients or endogenous substances are also carcinogenic *at* higher doses (see Appendix *IV* for a list of such claims). The presumption is that if substances are normally present, i.e., physiologic at certain tissue levels, they cannot also be carinogenic or otherwise harmful at the same or similar levels.

"There is no logical basis for such reasoning, and it most certainly is not supported by scientific evidence. In fact, analysis of the available data, substance by substance, clearly shows that evidence for a threshold cannot be derived from this reasoning . . . It cannot *a priori* be assumed that low levels of different substances, in bionutrients or otherwise, do not contribute, at least in part, to the existing incidence of human cancer. To the contrary, the unpredictable side effects of several drugs and food components suggest that low levels of certain nutrients and other substances probably do account for considerable disease burden in the population. This is particularly true if one considers the potential additivity of synergistic capability of many substances." (Squire and Goodman, P.H.C., p. 1–2).

Dr. Squire then carefully reviewed and catalogued the proffered evidence found in the Record in considerable detail (Appendix IV) and concluded that none of the cases provided evidence for thresholds. Dr. Squire reviewed the evidence for the carcinogenicity of number of the substances in question (cobalt, selenium, calcium, vitamin D2, tryptophane, indole, and eggs) and determined that the carcinogenicity of such substances has not yet been conclusively demonstrated. He stated that nickel and chromium were acknowledged bionutrients, but it was not known whether their carcinogenic forms were the same as their biologically necessary ones. The hormone, estrogen, presented the most completely documented case according to Dr. Squire. He pointed out that estrogen is an acknowledged bionutrient, an endogenous substance, and, yet, an established carcinogen. In addition, animal data (Heston, 1975) and human epidemiological data (Feinleib, 1968, Exhibit to Squire's Post-hearing Comments) both showed reduced frequencies of breast tumors in ovariectomized females, indicating that estrogens, even while performing their necessary biological functions at physiological levels, simultaneously contribute to the "background" incidence of breast cancer. The risks appear to rise continuously with dose without any evidence of a threshold.

Dr. Rall concurred with this interpretation:

"I know of no biochemical or physiological principle that indicates there is any reason to believe that. I find it much more comfortable scientifically to believe that they are indeed carcinogens, even at that concentration which is a biological necessity.

"I think the critical point is that chemicals are not known to induce any tumors that do not naturally occur. Therefore, some of the background incidence of tumors, cancers in the population may well be due to these critical, important, necessary trace elements, hormones, and so forth. That, to me, bears no relationship to the threshold hypothesis." (Rall, Tr. 374–375)

The idea that these essential bionutrients might at least in part, account for the "background" occurrence of cancer was supported by others. Dr. Benjamin L. Van Duuren (NYU) stated:

". . . there are certain chemicals which are natural body constituents that can cause cancer, and that is why there is a certain incidence of spontaneous cancer." (Van Duuren, Tr. 1851)

Dr. Lawrence Fishbein (NCTR) concurred (Fishbein, Tr. 1889).

Drs. Squire and Goodman offered the following summarizing comments:

"In the preceding pages, the inability to demonstrate a threshold was based upon a lack of adequate evience for carcinogenicity, or, with the exception of hormones, lack of evidence to demonstrate that certain carcinogens are also required nutrients or endogenous substances. In the case of hormones, the evidence shows that normal, endogenous substances may also contribute to cancer development, and there is no basis to conclude that the same phenomenon does not apply to other physioiogical substances. Primarily, however, one fundamental issue prevails, i.e., without specific supporting evidence, there is no logical *a priori* basis for concluding that because something is required or beneficial for some specific function, it cannot also be harmful or carcinogenic." (Squire and Goodman, Post-hearing Comment, p. 14)

Finally, Dr. Saffiotti (NCI) also reviewed this hypothesis, drawing similar conclusions:

"The specific examples used by Dr. Olson were those of selenium, chromium, nickel and of steroid hormones. The argument appears to be a logical non-sequitur. The fact that a substance is essential to normal body functions at a certain level in no way precludes the possiblility that this substance may under certain circumstances also enter into particular chemical-biological reactions which induce specific damage to certain cells, such as neoplastic transformation. The best example to illustrate this point is the case of estrogens (cited by Dr. Olson himself). It is well known that a normal level of these hormones indeed causes the induction of mammary tumors, as known by the fact that reduction of the levels of these endogenous hormones by ovariectomy leads to a marked reduction of the "spontaneous" incidence of breast tumors. This phenonemon has been shown not only in experimental animals but also in human females. Another relevant example is that of sunlight, which under

"normal" conditions is beneficial or even essential and is well tolerated by populations with highly pigmented skin. The same level of sunlight, however, is associated with a definite skin cancer incidence in light-skinned populations and results in an extremely high incidence and mortality from skin cancer in individuals with a specific genetic predisposition (*Xeroderma pigmentosum*). The same general argument applies to the cases of selenium, chromium and nickel, but in these cases, it has not been established that the chemical compounds of these elements which are essential are in fact the same as those discussed as carcinogenic. The evidence for carcinogenicity of selenium has been reviewed by the IARC and considered inconclusive (IARC 1975; NAS, 1976). The evidence for the carcinogenicity of chromium and nickel is limited to some specific compounds (IARC 1973, Vol 2; 1976, Vol 11). The chemical relevance of this evidence to the mechanisms of physiological action of chromium and nickel is uncertain, and it seems unlikely that the same compounds would be involved.

"Other witnesses in the hearing have cited other compounds in this context, such as tryptophan and its metabolites for which carcinogenic effects are experimentally well documented; for these compounds—as discussed above—there is no evidence on which to assume that they do not ever exert any carcinogenic effect at "normal" levels in humans.

"A few other compounds, discussed in the record of the hearing in this context, are Vitamin D, Vitamin A, calcium, cobalt and lactose. The evidence for the carcinogenicity of these agents is either inadequate or highly questionable. They do not pose any different problem than those reviewed above.

"In conclusion, the data available on the carcinogenic activity of compounds which are considered as essential nutrients or body constituents does not warrant any general inference that population thresholds can be determined for chemical carcinogens." (Saffiotti, Post-hearing Comment, pp 1–3)

OSHA concludes that it is not logical to assume that there must be thresholds for "bionutrients". Indeed, OSHA believes that there is substantial evidence in the Record showing that such thresholds probably do not exist.

4. Are there theoretical reasons to expect that a threshold exists at the cellular level?

Several witnesses presented a theoretical argument that a minimum number of molecules—about 10,000—of a toxicant must be present in a cell before any biological effects could take place: Dr. Robert Scala (Exxon), S. 11–12; Dr. George Claus (AIHC), S. 22–27; Dr. Robert Olson (St. Louis Univ.), S. 29–33; Dr. Bernard Oser (AIHC), S. 4–5; and the AIHC Panel on Alternatives, S. A–4. All of these arguments referred directly or indirectly to a paper by B. D. Dinman (1972), who reviewed data on dose-response relationships for enzyme inhibition and concluded as follows:

"Hutchinson in a perceptive essay has proposed the concept that there might be a concentration limit below which biologically significant reactions probably would not occur."

* * * * *

"Obviously the construction of a satisfactory stochastic model is beyond our present capabilities. But if we use the approach suggested by Hutchinson, it would apparently be reasonable to suggest that, "there might be too many commoner, accidentally and potentially interfering materials (or sites?) around in the cell for any very important substance to work practically at a concentration of less than 10^4 atoms or molecules per cell".

". . . To believe that a single molecule's presence in a cell implies a definite potential for deleterious effect disregards stochastic consideration. To believe that such molecules cause an undesirable effect disregards the presence of multiplicity of interfering substances. Such thinking also does not take into account the fact that the dose of a foreign atom may be related to the probability of its interacting with an available active site or that a similar probability governs the answers to the question of whether interactions will occur at discrete topographical loci upon a structural or functional molecule (or on a possible precursor). While the construction of stochastically sound model is remote, the reasonableness of the hierarchy of cellular element concentrations as these relate to metabolic function suggests that a threshold for biological activity exists within a cell at 10^4 atoms."(Dinman, 1972, pp. 495, 497; Exhibit 7 to Scala Statement)

No evidence was presented in the Record that this argument has any relevance to carcinogenesis. Dr. Dinman's original paper presented data only for enzyme inhibitors. Drs. Olson and Claus cited evidence only for enzyme inducers, hormones, and vitamin B 12 (loc. cit.). All these agents affect macroscopic functions of the cell, and there is no scientific reason whatsoever to extrapolate from such data to events such as reactions with genetic material. At a recent symposium, Dr. Marvin Schneiderman (NCI) addressed this issue and commented as follows:

"First, cancer appears often to be a disease of DNA damage or mis-repair, or incomplete repair and there is evidence that large numbers of molecules of an offending agent are not needed to cause DNA damage." (Schneiderman et al., 1978, p. 2; Appendix D to Schneiderman Post-hearing Comment)

Other reasons for regarding carcinogenesis as a phenomenon different from toxic effects such as enzyme inhibition were given above (subsection 1). Indeed, Dr. Dinman himself presented testimony in these hearings and did not make any claim that this argument would be relevant (Alcoa, Statement). Finally, even if the argument did apply to some class of carcinogens, it would have no practical relevance to OSHA standard-setting, because the hypothetical threshold concentration of 10^4 molecules per cell would appear to correspond to an extremely low level of exposure. For a substance of a molecular weight 600, it would correspond to only about 5 micrograms in a human liver, which could result from an occupational exposure to a concentration of less than 1 ug per cubic meter.

5. Have thresholds in fact been demonstrated for specific carcinogens?

Several witnesses claimed that thresholds had been observed for various carcinogens, but, in spite of questioning, only a handful of documented cases were proffered for the record. Dr. Paul Kotin (Johns-Manville) cited radiation, DDT, and asbestos as examples (Kotin, Tr. 8700; Kotin, Post-hearing Comments). The case of radiation has already been discussed above with citations to the work of Dr. Upton and the report of the Federal Radiation Council. The most extensive and detailed review of dose-response relationships for radiation carcinogenesis concluded that existing data could all be represented by a linear, non-threshold function (Committee on Biological Effects of Ionizing Radiation, 1972, pp. 86–87; Reference to Wilson Statement).

The case of asbestos was discussed in detail by Dr. Marvin Schneiderman (NCI):

"The authors say "The methods agreed in demonstrating a clear direct relationship, which may well be linear, between excess lung cancer mortality and total dust exposure. One of the discussants of the paper (Mr. G. Berry of the Medical Research Council of Great Britain), says "The way the x^2 statistics are presented (in Table 4) suggests that the authors were considering a threshold model, i.e. that there was no excess below some non-zero exposure. Certainly there was no detectable excess for an exposure less than 300 10^6 $pf^{-3}y$ but they obviously do not attach too much weight to this since they remark in the summary that the relationship may well be linear. It is difficult to quarrel with this in view of the fact that the x^2 of 38.76 with 9 degrees of freedom may be subdivided into 38.00 with one degree of freedom representing a linear trend and 0.76 with eight degrees of freedom for deviations about the trend; this is almost too good to be true!" It seems to us that this excellent piece of work, with careful attention to problems of data collection and analysis, with a rather large number of cases and controls, further indicates the almost insurmountable problems in establishing threshold for humans. We find it impressive that no clear threshold has been shown for this, or any other human exposure studies." (Schneiderman et al., 1978, pp. 25–26;

Appendix D to Schneiderman Post-hearing Comment)

Dr. William Nicholson (Mt. Sinai School of Medicine) also discussed the case of asbestos at length (Nicholson, Tr. 1706–1712), with similar conclusions:

". . . we cannot establish thresholds for cancer, whether for asbestos, as has already been discussed, or for other carcinogens." (Nicholson, Tr. 1706)

For DDT, carcinogenic effects have been demonstrated in animals at the lowest doses tested, and there are no adequate epidemiological studies (IARC, 1973, vol. 5, pp. 108–109; NIOSH 1978a; see Chapter IV, *Evidence Derived From The Human Experience*, above).

Dr. Harry Demopoulos proposed cigarette smoke as a carcinogen for which a threshold had been observed (Tr. 5463). However, there are extensive data in the Record demonstrating a linear, non-threshold dose-response relationship for cigarette-caused lung cancer, down to a non-zero incidence in "non-smokers" (Doll, 1964, 1971; Whittemore and Altshuler, 1976; Figure 1 to McCann Statement; OTA 1977).

Dr. Robert Olson (St. Louis Univ.) claimed that thresholds had been established for "numerous biologically active compounds", but he cited few except for the so-called "bionutrients" (S. 32–36). In any case, as pointed out above, he used the term threshold synonymously with "no-observed-effect level" (S. 10). Dr. Paul Woolrich (AIHA) who proposed dimethylnitrosamine (Tr. 4286), and Dr. Francis J.C., Roe, who proposed cadmium (S. 24), also apparently were referring to "no-observed-effect levels," since the papers they cited provide no evidence of thresholds.

The issue of identification of thresholds from empirical data was put into scientific perspective by Dr. Charles C. Brown (NCI) in a paper referenced by Dr. Arthur Furst (Univ. of San Francisco):

"Thresholds may be considerd from two viewpoints—an "actual" threshold, which is an exposure below which any carcinogenic response attributable to the specific agent is impossible, and a "practical" threshold, which is an exposure below which an attributable carcinogenic response is highly unlikely . . ."

". . . Experimental or observational evidence of the existence of an "actual" threshold is usually presented in the form of a dose-response graph, in which the percentage of animals with tumors or the average number of tumors per animal is plotted against the dose of the carcinogen. Either the existence of doses that do not lead to an increase in tumor incidence over controls, or the extrapolation of such curves to low doses that apparently would result in no tumor increase, is cited as an indication of the existence of a threshold below which no response is possible. This type of reasoning is an exercise in self-deception.

"In the first case, failure to observe positive responses does not guarantee that the probability of response is actually zero. From a statistical viewpoint, zero responders out of a population of size N is consistent at the 5% significance level with an actual response probability between zero and approximately $3/N$ (e.g., when $N = 100$ and zero responders are observed, the true probability of response may be as high as 3%).

"In the second case, when an observed plot of dose against tumors is extrapolated downward to find a no-effect dose, it is assumed that the observed dose-response relationship, usually linear, will obtain throughout the entire spectrum of doses and that one threshold exists for the entire population at risk. The assumption of linearity throughout the entire dose spectrum can easily lead to erroneous conclusions." (Brown, 1977; reprinted with minor changes in NAS, 1977a; Appendix I to Rall Statement)

Finally, Drs. Marvin Schneiderman (NCI), David Rall (Director, NIEHS), Donald Kennedy (Commissioner, FDA) and Matthew Meselson (Harvard Univ.) referred to an extensive review of the world literature on dose-response relationships for carcinogens:

"*Threshold hypothesis.* This hypothesis assumes that there is a dose below which cancer induction cannot occur. An examination of published dose-response data for chemical carcinogenesis in laboratory animals provides no clear indication of a threshold for any carcinogen (Craig and Miller 1974). In a review of 151 dose-response curves, none was found to be clearly inconsistent in a manner suggesting a threshold with both the single-event and the probit hypotheses discussed below. Neither is there any adequate theory of chemical carcinogenesis that would require the general existence of thresholds. Thus, even if a threshold is postulated, there is presently no empirical or theoretical basis for determining the dose at which it may occur. Unless and until this can be done, the threshold concept does not provide a practical basis for risk estimation." (NAS, 1975a, P. 83; Appendix H to Rall Statement)

Dr. Meselson commented further:

"But the first is that I know of no publication in the entire literature on dose response of primary carcinogens that provides evidence for the existence of a threshold. I have asked toxicologists to send me publications with such evidence, and I have not received a single one. I have gone through the—as mentioned in the National Academy report that is part of my testimony—the dose response study by the Franklin Institute done under contract with the National Cancer Institute, in seeing there is not a single case, and they have tried to review the entire world literature on dose response, 150-some odd dose response curves are reviewed in that study. I have not seen a single case in which the data depart significantly from the either probit or single particle hypothesis in a way demanding a threshold." (Meselson, Tr. 1545)

OSHA believes that, based on this testimony and the other evidence in the Record, no threshold levels should be presumed to exist for regulatory purposes at the present time.

6. Is there a consistent relationship between dose and latent period that would result in a practical threshold at low doses?

A number of witnesses presented an hypothesis that there is an inverse relationship between the dose of a carcinogen and the latent period for development of the consequent tumors, such that at sufficiently low doses, the latent period would exceed the lifetime of the animal and no tumors would be manifested. The corresponding dose would then be regarded as an "effective" or "practical" threshold. This argument might also be characterized as the "You shouldn't live so long" theory. This hypothesis is derived ultimately from the work of Druckrey who presented his results in the form of the following empirical generalization:

"In conclusion, the results of the quantitative experiments presented here conformingly show that also in carcinogenesis at continuous exposure with all substances tested and without regard to the organ of tumour development, clear dose-effect and time relationships exist, which are explained by the general formula

$$dt^n = \text{const.}$$

(10) with $n > 1$. Accordingly on logarithmic coordinates linear regressions are obtained. Even in the range of very small doses d no deviation from linearity is recognizable. There is no indication for the existence of a "subthreshold dose" as far as the primary effects on the cellular level are considered.

"Formula (10) proved to be valid not only in animal experimentation but also in human cancer statistics as demonstrated by Nordling (1953) and by Doll (1963). The numeric value of n, however, differs considerably with different carcinogens ranging from 1.1 up to 6.5 and can be considered as an indicator for the carcinogenic activity of the individual compound." (Druckrey, 1967, p. 75; Exhibit 8 to Scala Statement).

This generalization was narrowed by the late Dr. Hardin B. Jones (Univ. of San Francisco), who presented the following conclusion:

"Both threshold and non-threshold patterns of dose-effect relationships show a further influence of dose on risk of cancer in that the time to the appearance of cancers (the "latent period") increases as a fractional power of the reduction in exposure. When degree of exposure to a carcinogen becomes sufficiently small, the risk of cancer may become zero because there is not enough time, within the life span, for any cancers to develop. (Jones, S. 3)

Dr. Jones supported his conclusion with some documentation (Jones, Appendix B) and the following argument:

"It is not practicable to determine just when the initial carcinogenic change takes place even when there is a single exposure to a carcinogen, and the starting point is even more uncertain when there is chronic exposure to a very low environmental level of the carcinogen. It is also difficult to determine the exact point at which a viable tumor has evolved; that should be the endpoint, as the former is the starting point, for the measurement of what is commonly called "the latent period for carcinogenesis". But even with relatively crude boundaries of the latent period, it turns out that a general law governs its relationship to dose. If a dose, D_o is associated with a latent period, t_o for a given species of animal and a given carcinogen under specific conditions, then the latent period, t, associated with another dose, D, can be expressed as:

$$t=t_o(D_o/D)^n$$

and n usually has a value close to 3."

"This is a relationship that lends to a linear graph when plotted on log-log paper. The following examples show the generality of the power relationship between dose and time, and the possibility of simple extrapolation, in graphic analysis of the relationship, by prolonging the straight line. A statistical association of mathematical formulation, however, is of little force without a sound explantion of a way the relationship has come about as a biological response. Alexander Grendon and I have proposed the hypothesis that the carcinogen generates a fairly uniform density of initially altered cells in the tissue of concern, but that the affected cells result in tumors only if two or more clones that develop from them grow to a point where they make contact. We have postulated that it requires interaction of some unknown number of affected cells to generate an autonomous tumor. If the density of intitially altered cells is proportional to dose, as indicated by the tumor-dose relationship, then the mean distance between any two adjacent altered cells should be proportional to the cube root of dose. If the rate of growth of the individual pretumorous clones is uniform, the mean values of the time for adjacent clones to join should be inversely proportional to the cube root of the dose of carcinogen. Probably very few of the clones survive to reach this stage because of modifying factors, including those that relate to the defense mechanisms of the body against tumor formation. Thus, the actually measured dose-time effect will vary from the inverse cube root of dose. Instead of n=3 in $t=\text{constant}/D^{1/n}$ may be some value such as 2.4 or 3.5, etc.

"Linear extrapolation of dose and yield of tumors may theoretically indicate that N cases of cancer may result from even trace amounts of a carcinogen in food. In this case the risk is assumed to remain unchanged per unit of exposure form the high levels inducing tumors in experimental animals to the dilute residue in food. Linear extrapolation of the dose-latent period graph, however, indicates that these theoretical cancers would appear long after the maximum life span, so that, in fact, the hazard at trace residue levels is negligible or perhaps truly zero." (Jones, S. 14–16)

Dr. Jones's contention that the exponent "n" is usually equal to or close to 3 is not supported, however by the data cited in his own Appendices. As shown by Druckrey (1967), the value of "n" may vary between 1.1 and 6.5 for the chemicals he studied. Moreover, Jones and Grendon (1975) cited two cases in which n was infinite, i.e., the latent period was independent of dose (diethylstilbestrol at low doses, and urethane).

Nevertheless, Dr. Jones's conclusion was used by a number of witnesses to argue that the dependence of latent period on dose would suffice to ensure a practical threshold dose, below which no tumors would occur in the lifetime of exposed animals. One such argument was the following:

"(3) As the dose of a carcinogen is decreased, the latency period for cancer development increases. This phenomenon was revealed lucidly by Druckrey (1967), who noted that the does multiplied by some power of time was constant; i.e. $dt^n=$constant in which n=2 to 4. For all practical purposes, this relationship implies a threshold in that multiples of a lifetime will be required for expression of cancer in response to low doses. Albert and Altshuler (1973) utilized the increasing latency with decreasing dose of a carcinogen to formulate limits for unavoidable exposures to carcinogens.

"(4) Utilizing the relationship of dose to time-of-appearance of cancer, Jones and Grendon (1975) postulated that a number of cells in close proximity require transformation to allow development of an aberrant clone of cells and ultimately cancer. This multihit hypothesis, if true, will result in a marked reduction in the incidence of cancer as the dose is decreased for the same reason that trimolecular chemical reactions become negligible as the concentrations of the reactants are decreased." (Gehring and Blau, 1977, p. 166; Exhibit 9 to Hoel Statement)

The Council for Agricultural Science and Techonology commented:

"A fourth form of evidence is provided by the observation that the length of time between exposure and cancer development increases as the dose becomes smaller (Jones and Grendon, 1975). Extrapolation of such trends to doses lower than those at which cancer development is found experimentally leads to the inference that at suitably small doses the time between exposure and cancer development should exceed the lifetime of the species. According to such an extrapolation, the dose that corresponds to a lag time of one lifetime between exposure and cancer development might be defined as the threshold exposure for a single dose of a carcinogen." (CAST, S. 13)

Dr. Robert Scala (Exxon) pointed out:

"Jones and Grendon (1975) have suggested that the data on leukemia latency in survivors of atomic bombing and in humans exposed to radium from dial painting also lend themselves to comparable anaylses. For the radium painters, the latent period could be shown to be a function of a constant divided by the true radium equivalent; there is a practical threshold to the carcinogenic effect of ingested bone-seeking alpha emitters in that life ends for other reasons before radiogenic cancer can appear following small ingested doses. Jones and Grendon further point out that no experimental situations have been uncovered in which the relationship between latent period and carcinogenic dose was different for man from that for other animal species." (Scala, S. 15)

Reserve Mining Co. commented as follows:

"Finally, numerous animal experimentations have unquestionably demonstrated the existence of the dose-response effects of carcinogens. The experiments of Druckrey," and others, pertaining to numerous carcinogenic substances, have demonstrated the now accepted principles that the smaller the dose, the longer the time of cancer induction, and at very low dosages, the induction time can be longer than the life expectancy of the animal under investigation. These experiments amply demonstrate what has come to be identified as the "practical threshold level of exposure," i.e., the level of exposure which will not result in any carcinogenic effect within the life-expectancy of the subject animal." (Reserve Mining, S. 17–18)

However, a number of witnesses who commented on this issue showed that Druckrey's conclusion may not apply in general even to animal experiments, may not apply to cancers in humans, and cannot be used in the estimation of risks to humans exposed at low doses. In the first place, "latent periods" are difficult to define and to measure, particularly in extrapolating from animal experiments to humans (much less from one human group to another). Dr. Umberto Saffiotti (NCI) explained the difficulties as follows:

"The determination of latent period can be made by various techniques of observation in the course of a bioassay. If both test and control animals are sacrificed at a fixed time, only the early part of a temporal distribution curve may be observable, and consequently the estimate of the average latent period for all tumors or tumor-bearing animals may be artificially altered. If the test and control groups are allowed to live out their lifespan, the comparison of latent periods must take into account the relative survival and the number of animals at risk, particularly in the case of competing risks. A definition of latency period must be provided in the context of bioassay, and the methodology used for estimating it must be described. It is always difficult to determine the "onset" of a neoplasm. One can use morphometric criteria for tumors detectable during clinical

observation of the animals (e.g., skin or subcutaneous tumors) and establish a minimum size as a criterion for identification. For neoplasms of the internal organs it is practically impossible to determine an adequate "time of onset": methods such as palpation of the abdomen are highly subjective and generally unreliable. Large serial sacrifice studies can provide excellent data on time-to-tumor-induction, but they are seldom available and should not replace standard bioassay protocols. In most cases, what is referred to as "latent period" is the time between the beginning of the exposure and the time of observation of a tumor at death: this parameter is obviously influenced by all those factors which determine time of death, e.g., intercurrent disease or other tumors. Here too, the judgment of a competent pathologist will provide a critical evaluation of such aspects as tumor size, location, cellular differentiation and invasion which may contribute to an estimate of a temporal sequence." (Saffiotti, S. 26–27)

Dr. David Hoel (NIEHS) pointed out that the observation of a change in the time-to-first-tumor does not indicate any change in the actual latency periods:

"Unfortunately . . . the observed time-to-first-tumor will increase with decreasing dose for the multistage model yet no true threshold will occur at low doses with this model. In other words, a non-threshold model will predict that the data will look as through a threshold in time exists, when in fact it does not." (Hoel, S. 7; See also Tr. 2191–2196)

Dr. Hoel referred in this passage to a mathematical analysis by Guess and Hoel (1977), which was summarized as follows:

"A number of animal carcinogenesis experiments have demonstrated that the time from initial exposure to first detection of tumors increases with decreasing dose. This observation has led to some speculation that at very low doses tumors would take so long to develop that life would end before tumors appeared. We show that the apparent increase in tumor development time can be easily seen as nothing more than a manifestation of the mathematical fact that decreasing the incidence necessarily increases the first time-to-tumor. No physical increase in tumor growth time need to be postulated to explain the observations. Existing methods of low-dose risk extrapolation implicitly account for the increase in time-to-tumor statistics insofar as they account for the decrease in tumor incidence." (Guess and Hoel, 1977, p. 279; Exhibit 12 to Hoel Statement)

Mr. Richard Peto (Oxford Univ.) also showed that the conclusion that latent periods lengthen with decreasing doses is an error of interpretation:

"This dependence of time to *first* tumour, under conditions of *strong* carcinogenesis, on the applied dose level has been the source of a great deal of misleading confusion, as may be seen, for example, in the testimony of the late Professor Hardin Jones and in the testimony of Dr. Weil. The point is that the doses given in these experiments were so high that, had we been able to excise each tumour as it arose, each animal would in expectation have developed several tumours during his natural lifespan. If an animal would have developed several independent excised tumours, each with a similar age distribution, then what Blum or Druckrey would observe would only be the first of these several excised tumours. As with decreasing dose fewer tumours per animal arise, so the expected time of the first of the tumours excised from this animal would increase even if there was no dependence on dose of the age-distributions of the tumours which do arise. However, in this case the time increase will not continue indefinitely; if the expected number of tumours per animal is only 0.1 for example, then so few animals would get 2 or more tumours that the effects of the first tumour obscuring later tumours will be negligible, and at all total incidence levels below 10% there will be no further appreciable effect of dose level on the effects of competing to be first on the age distribution of those tumours which are observed. It is noteworthy that if Armitage and Doll's (1961) multistage model of cancer is accepted, leading to an incidence rate of cancer among cancer-free survivors which is proportional to $(d+d_o)^n$ $(age)^k$, then Blum (1959) and Druckrey's (1967) quantitative results—median proportional to $(d+d_o)^{(n/1+k)}$ and constant variance of the logarithm of tumour induction time—would be predicted, as would my initial principles. (This doesn't prove my principles, but it does prove that Blum (1959) and Druckrey's (1967) experimental results support them.)

"Thus, even if, as may well be the case, the age distribution of tumours is really independent of dose (and the effect of increasing dose is simply to increase the number of such tumours that would be expected to arise on each animal), one would expect that at high doses the *first* tumour would arise earlier, simply because the first of ten similarly distributed tumour times is likely to be smaller than the first of only two such times.

"Failure to allow for the numerical effects of competition to be first (and the consequent failure to realise that such a competition ceases to have any material effects once the expected number of tumours per animal decreases below about 0.1) is a common error (Jones and Grendon, 1975; 1976). A much more common, and much more serious error, is failure to remember that no carcinogen acts alone, and that the effects of background processes place another substantial constraint, completely ignored in the testimonies of Professor Hardin Jones and Dr. Weil, on the effects of progressive dose reduction on the age distribution of those tumours which do arise. As I have already explained, the simple assumption of the existence of some background exposure suffices to demonstrate that all mathematical and biological hypotheses yield predictions which conform with the principles with which I started: proportionality of extra risk to applied dose, and independence of age distribution from applied dose." (Peto, Annex B, pp. 6–7; also see Tr. 2527, 2531)

Dr. Meselson pointed out another mathematical problem arising from the statistical assumptions made by Druckrey (1967) and workers who quoted him:

"Assuming a log normal distribution is not something you would do on biological grounds, you do this on statistical grounds because it is a very easy function to deal with as a statistician, whether you are talking about railway train waiting times or cancer or anything. It is a statistical device, but it has built into it certain very unbiological characteristics. For example, a log normal distribution of time to tumor means that if you can get past a certain age you are home free; the danger starts to decrease. Everything we know indicates that the longer you are exposed to a carcinogen the hazard goes up; never comes down. Whereas, a bell-shaped curve, which is what they were talking about, of time to tumor, going up and then coming down, is a totally unbiological concept. It was used, I would gather although I have never talked to the authors about it, as a plausible statistical modeling device, but I think a not very satisfactory and not very biological one. There is reasonably good experimental evidence, in fact, that . . . the time distribution of tumor is independent of dose, unless you go so high as to start killing off animals, and instead takes this form that I mentioned before; namely, that for a steady product exposure to a carcinogen the likelihood of tumor goes, as the duration of exposure, to a power like three, four or five. That fits the results of Druckrey in Germany looking at a variety of compounds; it fits the human data . . ."

"So I believe that there is no basis whatever for assuming that the age distribution would be changed by the dose. So that if you give a little bit of a carcinogen and you find that the age distribution is a certain one—let's say that half of the tumors are in people 50 and lower and whatever—that if you give more of the carcinogen it will still be true that half of the induced tumors are in people in that age group and lower, that age distribution will not change unless, of course, you give so much that you begin wiping out the oldsters so there are no oldsters to contribute to that category." (Meselson, Tr. 1533–1535)

Finally Dr. Marvin Schneiderman (NCI) pointed out that the Druckrey-Jones argument is concerned only with the median time-to-tumor in a population, and that some individuals in a population will develop cancer early even when the median time-to-tumor is greater than a lifespan. Dr. Schneiderman also pointed out observational evidence that in the human population the age-distribution of many cancers does not appear to be dependent in any way on exposure to environmental factors:

"I believe that we will find many more situations similar to the radiation-breast cancer situation in which some external environmental event prepares the way for the development of cancer in later life when some other event either "internal" or external, but operational only at or after

some later age, takes place. For single stage cancers or cancers for which the second stage (or the necessary later stages) is not age-related, then higher doses of the initial exposure should lead to the shortening of the so-called latent period.

"One of the lessons that we could learn from the history of the cigarette smoking-cancer conflict lies right here. Early on, one of the counter arguments to the suggestion that cigarette smoking led to lung cancer was the observation that the average age of onset of lung cancer was only trivially lower in heavy smokers than in light smokers and non-smokers. The argument derived from the fact that Druckery had shown that with some chemical agents which produced cancer in a high proportion of the animals on which they were tested, the animals at the higher doses had shorter times before the cancers appeared. What was not realized was that the development of lung cancer is most likely a multi-stage event in which the cigarette smoking does not provide the last event (or does not often provide the last event). If the last event, the triggering event, comes from something within the individual (or outside him) which is not likely to occur until some later age, then we should expect only little effects of the dose of the agents leading to the earlier event(s) in reducing the time to appearance of the disease.

"That there is some host mediated later event or events is consistent with the fact that cancers in different organs in humans appear at different times in the life of humans. Cervical cancer in women occurs, on the average, at much younger age than ovarian cancer. Lung cancer occurs on the average of a younger age than bladder cancer. Cancer of the prostate is an old man's disease (See Axtell and Murray on the average age at diagnosis and years of life lost to cancers).

"It seems to me that the Druckrey model is meaningful only for single-event cancers, cancers caused by "complete" carcinogens to which no further contribution from the inside world of the host, or the outside world of other events, is necessary. I suspect that our animal model systems are most able to pick up only these one-step or complete carcinogens." (Schneiderman, S. 14–15)

In discussing the Druckrey model during his oral testimony, Dr. Schneiderman (NCI) concluded:

"The consequence of this—then one of the ways to check out on this would be to look at the average age of appearance of cancer, average age of diagnosis of different forms of cancer in which the incidence has been changing very rapidly. If the incidence has been changing, if cancer is an environmental disease, we would assume with increasing incidence there must be more exposure, heavier doses. The average age then ought to go down. If incidence is decreasing, we ought to expect there is reduced exposure. If there is reduced exposure, lower doses, the average age ought to go up. This has not happened. When one looks at the average age, at the diagnosis of cancer in the United States—at least I have the data for the United States, these average ages have not changed substantially. This again leads me to believe that the Druckrey model is not particularly applicable to most of human cancers. There may be some situations in which it is applicable, but to most of human cancers, it is not applicable. So that is that next section of review, my report." (Schneiderman, Tr. 710–712)

In a post-hearing comment, Dr. Schneiderman (NCI) provided further discussion of how changing the median of a distribution does not greatly influence when cancers are actually observed.

"This formulation does not address when the earliest cancers appear but only the median time to appearance. One needs, in addition, information on the distribution of time of appearance to evaluate the concept of a "practical" threshold. If the distribution is narrow in time, the concept may have meaning. If the distribution is broad, it will not be meaningful. One might expect in genetically heterogeneous animal, like man, that the distribution will be broad.

". . . We show that to reduce the average age at cancer death (of those people who will die of course) by one year (in the United States, the average survival from time of diagnosis of cancer is about 2 years) from 69.23 years, when the lifetime probability is .0014, i.e. the probability of cancers as rare as the breast in men or the tongue in women) to 68.2 years requires an increase in the cancer rate to a 11.16% lifetime probability—higher than that for any single cancer in the United States. The median age, in the absence of competing causes of death for a lifetime risk of .0014, is 194 years, and for a lifetime probability of .011 is 128 years (using the particular model of response we set out earlier). Thus the "practical" suggestion of reducing median cancer age to well beyond the human life span seems to be unrealistic, because it is not median age (in the absence of competing risks) that is important. The extrapolation models based on median ages are not appropriate."

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"All this leads us to say once again that there appears to be little or no evidence that the interpretations placed on the Druckrey model are correct when the incidence rates are low as they [are] in humans. If the model doesn't apply when the rates are low, then it certainly doesn't apply when one discusses "practical threshold" where the rates should be approching zero. The concept of the "practical threshold" impresses us as a will-o'-the wisp."

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"The time-to-appearance models that lead to considerations of possible "practical" thresholds are defective (or least unrepresentative) in at least two ways: first they deal with high incidences of cancer in test animals while the lifetime probability of cancer in man is low for any site. With low incidences median ages to appearance are trivially dose related. The human data within the United States show no dose-median age relationship. Second, the apparent relationship between dose and latent period may be an artifact of high doses producing many tumors per animal the first of which having a competitive advantage will kill the host, before the others can become clinically noticeable." (Schneiderman et al., 1978, pp. 7, 28, 33, 37: Appendix D to Schneiderman Post-hearing Comment)

7. *Would the interaction among carcinogens invalidate the concept of a threshold?*

A number of witnesses testified that, even if thresholds could be established for the circumstances in which animals are exposed only to single carcinogens, this would have little or no relevance to risk assessment for humans, who are exposed to many carcinogens, either simultaneously or sequentially. Specifically, several witnesses pointed out that there is already a relatively high incidence of cancer in the human population. Hence many individuals are already at or close to the "threshold" for certain processes involved in cancer development, so that incremental exposure to even small quantities of an agent that accelerates these processes would be expected to lead to an increase in the frequency of cancer. This point was discussed by Dr. Mathew Meselson (Harvard Univ.) as follows:

"More than that, one has to remember a very simple but for some reason until the last few years overlooked point, and I think a very powerful point, and that is as animals we humans are way past the threshold. We are like an experiment with mice or rats in which 25 percent of them are coming down with tumors. We are not a cancer-free population. We have an enormous incidence of cancer in our population. So that unless one is talking about a chemical which is being activated by an absolutely unique pathway unique to that chemical, an activating enzyme that does not work on anything else, or does something unique to the entity that no other chemical does, activates a mutagenic repair pathway that no other chemical does, unless that is the case, we are just talking about adding a little bit more when we talk about low dose, to what is already a lot, and demonstrably past the threshold, because we are already past any thresholds as a population.

"So to taken the burden on one's self of saying that I believe this chemical is unique in the world, is operating by a mechanism that is not already going on in our bodies, is an incredibly arrogant statement. There would be no basis in scientific fact for such an a priori statement. So it would be different if nobody ever got cancer, and some scientists came along and said, we have just discovered that there could be a disease if you let this certain thing in the environment. We are going to call it cancer. Then somebody could say, but how do you know there is not a threshold for this hypothetical disease that at pesent nobody is getting, because if nobody is getting it, clearly we could be below the threshold. That might be why nobody is getting it. But if 25 percent of us are getting it, you have to make some, in my opinion, very far out assumptions before you can conclude that a chemical under—a

particular chemical under scrutiny is going to operate in such a way as to not already be past that hypothetical threshold." (Meselson, Tr. 1545–1547)

Dr. David Rall (Director, NIEHS) made essentially the some point, both in his opening statement (Rall, Tr. 354) and in response to a question about protective mechanisms:

". . . I think however, it becomes almost ridiculous when you recognize that 16% of the people in this room are going to die of cancer. I mean, this talk of a threshold is, to me, sort of an ethereal dream world. You know, 16% are going to die of cancer and about twice that will get cancer in their lifetime. I am sorry, but I think the threshold was exceeded a long time ago, and I just do not see any point in talking about it anymore, in terms of the population." (Rall, Tr. 397–398).

Mr. Richard Peto (Oxford Univ.) developed this point at some length in his direct statement (S. 5–10 and Annex B) and presented a mathematical proof that under rather general conditions no threshold would be expected. The basic requirement for this proof is the existence of "carcinogenic background alternatives", i.e. the existence of other agents in the environment of the exposed animal which give rise to the same functional effect:

"The second assumption needed is that some carcinogenic background alternatives exist to the carcinogen being considered, i.e. *some* of the spontaneous cancers that arise do so by mechanisms which are functionally similar to those whereby the test carcinogen works. Again, I believe that for *most* carcinogens *some* carcinogenic background alternatives are likely to exist, although again I would expect a few counter-examples to occur. (The counter-examples would probably involve cases where the carcinogen produces some gross pathological effect, such as suppression of ovulation, which then affects cancer risk, rather than cases where it acts directly by causing a local DNA lesion.)" (Peto, S. 6)

In introducing this section of his testimony, Mr. Peto explained that most arguments for the hypothesis of thresholds or extremely low risks associated with low doses are due to failure to recognize the possibility that "equivalent background" may exist. Accordingly, he referred to the concept of thresholds as "nonsense" (Peto, Tr. 2515).

Many witnesses presented examples of experiments which had demonstrated additive or synergistic effects of different chemicals. Dr. David Kaufman (Univ. of N. Carolina) testified about his own experimental work with combinations of chemicals and drew the following conclusions:

"Our work shows that treatment of experimental animals with two carcinogens given sequentially can result in an increase in tumor incidence and a decrease in time necessary for the appearance of tumors of the respiratory tract. In accord with our findings, the several cited examples of work by others show that in an analogous manner combinations of carcinogens can produce tumor incidences greater than that expected with either of the single treatments or that anticipated as the sum of the effects of the single treatments. The examples cited indicate that this type of interaction can be demonstrated in tissues other than the respiratory tract and in experimental animals other than the hamster as well as *in vitro* studies. Furthermore, I have cited examples where combination of carcinogen exposures in humans also produces a greater than an apparent additive tumor response." (Kaufman, S. 19)

Dr. Richard Griesemer (NCI), too, testified that synergism among carcinogens was a frequent phenomenon:

"I recently went through an exercise of attempting to find good examples of additive effects from combinations of chemicals, and I had discovered that by and large, the evidence is for something more than additive, either, that is, multiplicative rather than additive, or on the opposite extreme, some combination effects are inhibitory." (Griesemer, Tr. 928).

Dr. Robert Squire (Johns Hopkins Univ.) referred to many examples:

"Numerous experiments involving cocarcinogenesis indicate that different carcinogens may have additive, synergistic, or antagonistic effects in organisms exposed to them. It is unlikely that we can predict which, if any, of the above effects will occur in the case of specific chemicals without observing their action experimentally, but numerous studies do demonstrate the existence of potential hazards.

"Epithelial cancer, for example, as is now recognized, involves a multistage process in which sequential cellular and subcellular events precede the appearance of clinical cancer. To describe this process, the concepts of "initiation" and "promotion" have been introduced in studies of carcinogenesis in skin (Berenblum 1941). These prevail today and are considered relevant to many other epithelial systems (Farber 1976; see also Appendix B). "Initiation" describes a specific, irreversible cellular alteration induced by carcinogenic substances and resulting in a population of latent or dormant tumor cells. "Promotion" describes the proliferation of those cells which is induced by subsequent exposure to the same or a different substance and which results in a progression to clinical cancer. Classical initiation-promotion studies illustrate well the synergistic effects of separate exposures neither of which alone would have produced cancer at the doses involved. Significantly, the conditions induced by initiator substances persist, and therefore exposure to a promoting substance even after a considerable delay can result in cancer (Berenblum 1974; Boutwell 1974, 1976, 1977).

"Studies involving liver carcinogenesis have also shown persistent and additive effects of subcarcinogenic exposure to certain substances. Becker (1975) demonstrated that cellular alterations induced by subcarcinogenic doses of N-2-fluorenylacetamide may later be augmented by subcarcinogenic doses of dimethylnitrosamine or N-hydroxyfluorenyl acetamide to yield hepatocellular carcinoma. Weisburger et al. (1965) showed an increase in liver cancer induction after combined exposure to 2-acetylaminofluorene and carbon tetrachloride.

"In other systems, the studies of nitrosomethylurea and cyclamate by Hicks et al. (1975) and the Oser study (Oser et al. 1975) of cyclamate and saccharin demonstrated at least additive if not synergistic effects of two substances in the induction of bladder cancer in rats. Laskin et al. (1970) demonstrated that benzo(a) pyrene combined with sulfur dioxide, when inhaled, induced lung cancer in rats. In the doses administered, neither substance alone was carcinogenic.

"Other examples of cocarcinogenesis in animals exist in the literature; there is also evidence that cigarette smoking and occupational exposure to asbestos have synergistic or additive effects in humans (Selikoff et al. 1968). It must therefore be assumed that cocarcinogenesis is not rare in humans or animals." (Squire, S. 5–7)

Studies by Dr. Irving Selikoff (Mt. Sinai School of Medicine) on the interactions between the effects of asbestos and smoking were discussed by Dr. Weinstein (Columbia Univ.), Dr. Nicholson (Mt. Sinai School of Medicine), and Dr. Harris (NCI) as well as by Dr. Selikoff:

"We found that among the 2,066 non-cigarette smokers there should have been, the way the statisticians put it, 1.82 deaths of lung cancer. There were eight. In other words, somewhere around four to five times as many. But this is certainly not a major public health problem. You had four times or five times the number of a very small number; and five times nothing is still not very much.

"On the other hand, you had again five times the already high risk of cigarette smoking, so that instead of 67 deaths anticipated, 325 actually occurred, confirming not simply the carcinogenicity of asbestos in terms of lung cancer among those exposed, but also the extraordinary multiple factor etiology. (Selikoff, Tr. 1702)

Dr. Selikoff also mentioned the interaction of radiation and benzene:

"For example, to revert to Japan, where we know that radiation-exposed people there have more leukemia than anticipated. But if, after Hiroshima and Nagasaki men were exposed to benzene in their work, they have much more leukemia than all other Nagasaki and Hiroshima victims. So the potential for multiple factor interaction which our colleagues in the laboratory have been prodding us about for these last 20 years is now becoming very real." (Selikoff, Tr. 1748)

Additional discussion of the interaction between asbestos and cigarette smoke was presented by Dr. William Nicholson (Mt. Sinai School of

Medicine), Tr. 1713; Dr. Curtis Harris (NCI), Tr. 1973–1974; and Dr. Bernard Weinstein (Columbia Univ.), S. 7. Dr. Francis J.C. Roe (AIHC) also discussed the phenomena of tumor promotion, cocarcinogenesis, and additive and synergistic effects of carcinogens and gave additional examples (S. 41–44).

The practical implications of additivity and synergism were discussed by a number of witnesses. Dr. Richard Griesemer (NCI) commented as follows:

"One of the things that concerns me about the proposed regulations is that the emphasis appears to be on single chemicals and their carcinogenicity, where people are exposed to many chemicals at differing rates and differing amounts, and I believe that the combination effects are much more important than those of single chemicals." (Griesemer, Tr. 938).

Dr. William Lijinsky (NCI-FCRC) showed how additivity and synergism make the concept of threshold inapplicable:

"In the chronic tests of chemical carcinogens in animals we administer a single substance which is the only variable between a treated group and an untreated control group. We then measure the increased tumor response, if any, in the treated group compared with the control group. If there is a statistically significant increase in tumor frequency in the treated group, we say that the substance is a carcinogen. This is not, however, the way in which man is exposed to a carcinogen, even in the workplace. Man's exposure is to a multitude of carcinogens, arising from diet, habits and the environment, all of which contribute to the cancer risk which is so high that 1 in 4 of the population of the United States develop cancer of some type during their lifetime. Therefore, it is impossible to state that any exposure to a carcinogen is without risk, since we do not know how to measure this risk, nor what the other risks are." [Lijinsky, S. 16]

Drs. Crump, Hoel, and Bates and Mr. Peto placed similar comments in the Record. Dr. Kaufman also spoke very strongly for a cautious approach to regulation in this context:

". . . A variety of extrinsic and intrinsic factors can influence the development of cancer. Some of the examples considered experimental studies in animals, but it is likely that similar processes are operative in the causation of human cancer. The general agreement between the experimental studies considered and the human studies cited lend support to this assertion. It should be evident that carcinogenic risks for individual humans cannot be accurately estimated by simple extrapolation from animal carcinogenicity data. Other factors may influence the susceptibility of individuals to cancer. In fact, certain susceptibility factors may greatly increase the sensitivity of individuals to a given exposure to carcinogens. The conclusion which I draw from these observations is that in attempting to establish conditions which protect individuals at their place of work from cancer-causing hazards, other factors must be considered besides the risk from exposure on the job. An ample margin of safety must be included to provide for the effects of other co-carcinogenic or carcinogenic agents to which the individual is exposed as well as the effects of intrinsic properties of the individual which puts him at increased susceptibility. Although some types of exposures and some intrinsic properties of individuals may actually impede rather than potentiate the effects of carcinogen exposure, it is impossible to accurately predict these favorable interactions in all cases. Thus, prudent policy would include an effort to provide some protection from additive or synergistic effects." (Kaufman, S. 20)

Dr. Lorenzo Tomatis (IARC) also discussed this point:

"This hypothesis does not make prevention any easier. In fact, if it is very difficult to calculate a minimal or undetectable effect dose of a carcinogen acting in isolation, it becomes an almost impossible task to define a no-effect or minimal-effect dose of a carcinogen acting in combination with another carcinogen or with an agent which may modify its activity." (Tomatis, 1977a, p. 301; Appendix 3 to Tomatis Statement)

Dr. Donald Kennedy (Commissioner, FDA) commented as follows:

"The problem of thresholds is further confounded by our knowledge that there are synergistic and additive effects among carcinogens and that the human population is exposed simultaneously to a number of carcinogens. The problem of establishing a "safe" exposure level for individual carcinogens is greatly exacerbated because of this. I do not expect a satisfactory solution to this problem for many years." (Kennedy, S. 11)

Finally, Dr. Rall (Director, NIEHS) addressed the issue as follows in one of his exhibits:

"But the issue is not thresholds or no thresholds; it is one of adding a new carcinogen to a pool of present carcinogens. I would suggest, therefore, that there may well be thresholds with carcinogenic substances when given to a very clean animal in an environmentally controlled situation that is, when there are few or no other carcinogens present: this is what the experimental oncologist tries to create in the standard laboratory animal test system—a clean animal of known and homogeneous genetic background with a well characterized diet and no known carcinogens living in sterile filtered air. The human population is different, however: the mouse doesn't smoke or breathe hydrocarbons or sulfur oxides from fossil fuels, doesn't drink, doesn't take medicine, doesn't eat bacon or smoked salmon, but man does." (Rall, 1978, pp. 164–165; Appendix C to Rall Statement)

OSHA concurs with this summary of the evidence, that the exposure of humans to a variety of different carcinogens, which frequently have additive, synergistic or inhibitory effects, provides additional reasons to regard the concept of thresholds as irrelevant and inapplicable to the determination of human hazards or risks.

e. OSHA's Conclusions

After review of the very extensive evidence in the Record, OSHA concludes that its proposed position that there is no presently acceptable way to reliably determine a threshold for a carcinogen for any given population is amply supported by the evidence presented and also represents, to a large extent, a consensus of scientific opinion. Specifically, there is substantial evidence in the Record that carcinogenic processes differ from other types of toxic effects in being irreversible and originating from minute foci or even from single cells, so that there is no theoretical reason to expect a threshold even for an individual. The various defense mechanisms put forward as theoretical bases for thresholds, such as DNA repair, detoxification, and immuno-suppression, are unlikely to be efficient enough to ensure a threshold, as pointed out below. And, even if thresholds do exist for individual humans, it would not be expected that such thresholds exist for populations of exposed persons, because of individual human variations in susceptibility, additive and synergistic effects with other carcinogens and with intrinsic and extrinsic factors.* The evidence proffered for the existence of thresholds for specific carcinogens was inconclusive or erroneous. In short, there is much scientific evidence that thresholds do not exist for carcinogenesis; even if they do, there is no scientific way to establish what they are for any specific carcinogen and for any specific population.

Stated a different way, the self-replicating nature of cancer, the

*As pointed out, our inability, at present, to determine whether humans are more or less sensitive than any test animal species in question is one lynch-pin to the determination of thresholds. In the case of thalidomide, for example, admittedly not a carcinogen but a teratogen, humans were 60 times *more* sensitive than mice, 100 times *more* sensitive than rats, 200 times *more* sensitive than dogs and 700 times *more* sensitive than hamsters. In the case of inorganic arsenic, a known human carcinogen, no positive results have been reported in any mammalian test animal, including the mouse and rat, although non-positive results have been so reported. And in the case of beta-naphthylamine, a known bladder carcinogen in humans, monkeys and dogs, non-positive results have been reported in rats and rabbits. Hence, today it does not appear feasible to predict a quantitative finite "safe" level for a carcinogen to any individual human, let alone for a human population, comprised as we all are of aggregates of genetically heterogeneous individuals, with widely varying predispositions and susceptibilities and widely varying exposures to carcinogenic substances throughout our lives.

multiplicity of causative factors to which individual humans can be exposed, the possible additive, synergistic or antagonistic combination of effects, and the wide range of individual human susceptibilities work together in making it currently unreliable—and perhaps impossible—to predict a threshold below which any given working human population, exposed to a carcinogen, has no increased risk of contacting cancer. This was true in 1960 when Secretary Arthur Fleming of HEW testified that: "Scientifically, there is no way to determine a safe level for a substance known to produce cancer in animals". This was equally true, fourteen years later, when HEW Secretary Caspar Weinberger stated on June 14, 1974 that HEW "lacks the scientific information necessary to establish no effect levels for carcinogenic substances in animals in general and in man in particular. In the absence of such information, we do not believe that detectable residues of carcinogenic animal drugs should be allowed in the food supply." It was true in 1975 when the Director of NIOSH stated that: "It is not possible at present to determine a safe exposure level for carcinogens." (Revised Arsenic Criteria Doc., p. iv, 1975). And the Secretary of Labor believes it true today.

OSHA concludes, based upon substantial evidence in the Record, that observation of the marked individual differences in the response of humans to carcinogens shows that some individuals obviously do not develop cancer in their lifetime, whereas others develop it readily after the same exposure to the same carcinogen. Although these observations may be compatible with the existence of different "thresholds" for individual humans in certain conditions, they are not a basis for predicting a "no-effect", "threshold" or "safe" level of a carcinogen in other individuals exposed in the same or different conditions.

In addition, individual humans are generally exposed throughout life to a number of carcinogens, which may be considered to provide a background of some carcinogenic risk; exposure to any amount of a single carcinogen, however small, should be regarded as capable of adding to the total carcinogenic risk. Susceptibility to cancer can vary greatly among individual humans due to genetic, racial and ethnic factors, to environmental and dietary exposure and the other factors.

This variability among humans makes it very difficult to have a great deal of confidence that an observed "no-effect" levels of exposure in experimental test animals or even in a specific human population (for which individual variation may be small in comparison to the total population) will be applicable to any given human population at risk. A large number of factors (e.g., age, sex, race, nutritional status, immunologic status, general state of health, previous exposure to other substances) could affect individual susceptibility. Based on the very substantial evidence in the Record, therefore, OSHA believes that even if thresholds for specific carcinogens could be demonstrated for certain individual humans, no reliable method is known today for establishing a threshold that could apply to an exposed group of workers.

11. Should Criteria or Protocols Be Established for the Conduct and Interpretation of Carcinogenesis Bioassays?

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA stated that carcinogenicity results from testing in animals should generally be assessed according to sound and accepted principles for the design and interpretation of such experiments and that while there was substantial scientific agreement on what many of those principles are, that specified and rigid protocols for experimental design and data interpretation would not be prescribed by OSHA.

OSHA made clear its intention to rely upon scientifically sound and convincing positive evidence of animal carcinogenicity for classifying a substance as a potential human carcinogen. OSHA proposed to "rely on evidence from . . . . adequately designed and conducted animal studies . . . . as the basis for such regulation" (42 FR 54148). OSHA reinterated this intention to rely on ". . . . positive results in tests with proper statistical confirmation. . . ." (42 FR 54164). OSHA's proposal cited the 1969 NRC Food Protection Committee, which advised that:

". . . appropriate and well-executed animal studies are more likely to provide a substantial background of biological data from which to judge safety. . . ." (NRC, 1970, p. 1)

The importance of careful scientific scrutiny of reports of positive bioassay results was cited in the proposed regulation in a quotation from Dr. Umberto Saffiotti, who said, ". . . . some of the 'positive' tests reported in the literature—particularly the older ones—are not quite satisfactory by present standards. . . ." (42 FR 54152).

OSHA's proposal emphasized the need to evaluate positive bioassay reports in light of details of experimental protocols and interpretative procedures of the particular experiments in question. The proposal stated:

"OSHA recognizes that there are . . . factors involved in carcinogenicity tests which affect the degree of confidence in the results . . . . OSHA may require detailed review of each experiment before classifying each toxic substance . . . ." (42 FR 54165)

The proposal further stated that a prsumption of carcinogenicity shall be rebutted if "animal data . . . . are totally inadequate to establish any conclusion with respect to . . . . carcinogenicity . . . ." (42 FR 54185).

In the proposed regulation, OSHA recognized that general agreement exists in the scientific community on the criteria and basic principles for judging the acceptability of data from animal carcinogenicity bioassays. The 1969 Mrak Commission Report, for example, was cited in the proposed regulation on the point that there is a "remarkably unanimous view on the general principles and criteria to be followed in carcinogenesis safety evaluation, widely accepted in principle by the scientific community . . . ." (42 FR 54158). The 1970 Ad Hoc Committee Report to the Surgeon General was also cited:

"Several committees of experts in the field of carcinogenesis convened by national and international bodies over the past 15 years have formulated general principles for performance and evaluation of carcinogenesis studies in animals. The recommendations put forth by these committees have shown remarkable unanimity . . . and are widely accepted in principle by the scientific community." (NCI, 1970, p. 6)

The proposed OSHA regulation concluded that:

"[i]t would seem therefore, that opinions of scientific experts generally are substantially in agreement on . . . the minimal and optimal experimental conditions for testing for carcinogenicity . . . . (42 FR 54160)

OSHA's proposed regulation did not suggest or specify particular minimal or desirable criteria or standards for acceptance of evidence of carcinogenicity from animal bioassays. OSHA made clear in the proposed regulation that while there is substantial scientific agreement on what constitutes adequate carcinogenicity testing, particulars of experimental design and interpretation have not been and should not be rigidly standardized in order to select information relevant to regulation of substances posing a carcinogenic risk to humans. OSHA's proposal stated that:

". . . the general criteria and principles applied to the design and interpretation of studies in animals . . . illustrate the varying conditions accepted for testing for carcinogenicity in animals . . . ." (42 FR 54157)

As seen below, OSHA's avoidance of prespecification of particular minimal or desirable testing and/or interpretative protocols accords with scientific opinions of most experts appearing at the public hearing, and also accords with conclusions of previous scientific bodies.

A key point, made in the proposed regulation, is that there are necessarily different standards for judging the acceptability of bioassay results depending on whether or not the results indicate that the test substance is positive for carcinogenicity. Scientific groups responsible for judging the *safety* of substances such as food additives were cited in the proposal as delineating criteria for acceptable *negative* experimental evidence of carcinogenicity. Such negative evidence is required for approval of many substances for human consumption. The 1961 joint FAO/WHO Committee on Food Additives, for example, was cited as recommending standards for bioassay procedures, including numbers of animals, numbers of species, sexes, and doses, as well as the duration of bioassays for safety studies (42 FR 54158). Other previous scientific committees which specified factors for acceptability of safety tests were also cited, including the 1969 UICC Report and the 1969 Mrak Commission Report. These reports were published by groups concerned mainly with establishing minimal standards for evidence showing that substances are *safe enough* from the point of view of carcinogenicity for human consumption or exposure to be acceptable. OSHA, in contrast to these groups, is not primarily concerned with *negative* carcinogenicity data; instead, OSHA reacts to reports of *positive* evidence of carcinogenicity in order to protect employed persons from exposure to carcinogens. As discussed in the proposed regulation (42 FR 54161), substances for which there is negative evidence of carcinogenicity from animal bioassays would be treated in the same way as substances for which there is no evidence for or against carcinogenicity.

The proposed regulation indicated that positive and "negative" carcinogenicity results must be evaluated according to different standards. While certain basic criteria for the acceptability of positive bioassay data are necessary to avoid false positive conclusions, convincing evidence of carcinogenic activity can be derived from bioassays conducted according to a wide variety of experimental protocols. Standards for the acceptability of positive data cannot be defined in the same way that is possible in setting minimal standards for negative conclusions in safety testing of chemicals. This distinction was clearly reflected in the proposed regulation, which quoted the 1969 UICC report on this point:

". . . negative results of biological testing are less significant than positive results. . . . this is all the more true when testing procedures are inadequate." (UICC, 1969, p. 18)

b. The Public's Response and OSHA's Evaluation

(1) General Characterization of the Testimony.

The preponderance of expert testimony presented at the public hearing focused on four points: (1) carcinogenicity data have been generated in the past by a wide variety of experimental bioassay procedures, and such data must be carefully reviewed in order to be useful for regulatory purposes; (2) there is broad scientific agreement on criteria and principles for assessing the adequacy of experimental protocols for animal bioassays and the reliability of conclusions derived from such bioassays; (3) narrowly defined protocols or particular prescribed standards for bioassay execution should be avoided by OSHA; and (4) inferences of human carcinogenic risk should not be limited to experiments which have been interpreted by standardized procedures or protocols.

Several opinions were heard on factors which OSHA should take into account in judging the adequacy and reliability of animal bioassay data. Most witnesses described such factors in general ways and specifically advised against rigid standards for the assessment of bioassay results.

(2) Specific Issues Raised at the Hearing

The questions relating to adequacy of experimental bioassay protocols and results which were addressed at the public hearing may be summarized as follows:

a. Does OSHA need to review protocols of animal bioassays yielding evidence that a substance is carcinogenic?

b. Should OSHA prescribe protocols for the design and execution of carcinogenesis bioassays?

c. Should OSHA prescribe standards for the interpretation of bioassay data?

d. What factors need to be taken into account by OSHA in the interpretation and evaluation of animal carcinogenicity experiments?

e. How should OSHA judge whether positive bioassay reports meet its criteria for acceptability?

(a) Does OSHA need to review protocols of animal bioassays which yield evidence that a substance is carcinogenic?

Long-term animal bioassays for detection of carcinogenic activity are subject to a great many factors which may influence the results. As Dr. Walter Heston (NIH) testified, ". . . there are many important genetic and environmental factors which are known to influence the incidence of hepatomas and other tumors . . ." (S. 15). For this reason, OSHA intends to scrutinize bioassay protocols to establish whether any findings of carcinogenicity are reliable.

The need to subject evidence of carcinogenicity to scientific review before such evidence can be used for regulatory purposes was clearly stated in the OSHA proposal and reiterated by many witnesses called during the hearing. As Dr. Richard Bates (NIEHS; FDA) testified:

". . . evidence that [a] chemical has caused the cancer . . . requires an evaluation of the way in which the study was conducted and that [the study] was conducted adequately. . . . I certainly would not myself support the concept that you use just any set of figures that somebody puts in front of your nose for making a regulatory decision . . . you do have to evaluate whether [the] study was well conducted and well carried out. . . ." (Bates, Tr. 599–600)

Dr. Umberto Saffiotti (NCI) similarly advised:

"A chemical agent should not be judged carcinogenic solely on the basis of a cursory 'tumor count', without thorough evaluation of the conditions of exposure and of host response." (Saffiotti, S. 7)

Dr. Donald Kennedy (Commissioner, FDA) concurred:

"I support the position that no final conclusion about the carcinogenicity of a chemical should be drawn from poorly designed or conducted animal experiments." (Kennedy, Tr. 522)

Dr. Renate Kimbrough (CDC) agreed, ". . . how well the study was conducted . . . [could] make a lot of difference . . ." (Tr. 1796). Dr. William Lijinsky (NCI–FCRC) testified:

"It seems foolish to accept the results of any test which shows a negative result uncritically as proving the safety of a substance, and equally foolish to accept a positive result, i.e., evidence of hazard, uncritically as evidence of danger. Much depends on the quality of the test." (Lijinsky, S. 2–3)

Dr. Carroll Weil (Carnegie-Mellon) also supported the position that there is

a need to review experiments before results could be accepted:

". . . all experiments are not created equal. Differences in experimental design . . . may radically affect results." (Weil, S. 2)

Dr. Leon Golberg (CIIT) agreed:

". . . the full data forthcoming from each test will need careful evaluation in conjunction with all other relevant data by appropriate experts . . ." (Golberg, Tr. 6488)

Several witnesses testified that much carcinogenesis testing has been of varying, and sometimes poor, quality, emphasizing the need for review of experiments. Dr. Adrian Gross (FDA) testified that there have been ". . . widespread shortcomings in the . . . data submitted to [the FDA] for regulatory purposes. . . ." (Gross, S. 12). Dr. Gross added that not all the shortcomings were due to problems in experimental protocols or procedures:

". . . reports on results of animal testing are often false or misleading and in some cases they may be downright fraudulent" (Gross, S. 13)

Mr. Leslie Dach (EDF) testified that:

". . . there have been unfortunate experiences where federal agencies have gone out and asked for further followup studies, and they have come back in a form that was then unusable to the regulatory agency . . ." (Dach, Tr. 7341)

Dr. Sidney Wolfe (Health Research Group) stated that "none of these studies are perfect . . ." (Wolfe, Tr. 6537). Dr. Francis Roe (AIHC) added, "In some cases . . . the standard of execution of tests has been low." (Roe, S. 59). Dr. Golberg (CIIT) testified:

" . . . the protocols and conduct of bioassays carried out even in the recent past leave much to be desired . . . results cannot be taken at their face value for automatic decisions on their carcinogenic potential."

* * * * *

". . . we have data going back many years, and the standards of performance of toxicological tests were not as adequate then as we would have them today." (Golberg, Tr. 6487–88, 6500)

Dr. Roe agreed that test results need evaluation by experts of "many disciplines" and went on to allege that U.S. regulatory agencies do not engage experts to interpret bioassay data. Dr. Roe offered:

"The interpretation of long-term animal tests should not be left to lump-counters aided by computers and statisticians as tends to have become the norm in (r)egulatory (a)gencies within the U.S.A. (Roe, S. 62)

OSHA and industry witnesses agreed that deficiencies in past test protocols can be taken into account by experts to make valid judgments on the adequacy and reliability of the data produced by such experiments. Dr. Golberg noted:

". . . one is always able to criticize what was done in the past . . . utilization of that data is possible, provided that the people who are reviewing it are experts and have the necessary background and breadth of experience." (Golberg, Tr. 6500)

Dr. Bernard Weinstein (Columbia Univ.) voiced the same opinion:

". . . there will be experiments where the data is interpretable even though it may not fulfill the current NCI bioassay description." (Weinstein, Tr. 2258)

As explained in the proposed regulation, OSHA intends to act on reports of positive carcinogenic activity of substances. For this reason, evaluation of "non-positive" carcinogenicity results is of interest to OSHA in the limited areas discussed above and below, and where expert evaluation of results which at face value appear non-positive may in fact reveal positive evidence for carcinogenicity. Thus, in general, OSHA's review of bioassay protocols will be mainly concerned with verifying that results which appear positive are indeed reliable. In his oral testimony, Mr. Grover C. Wrenn, Jr. (OSHA) made clear OSHA's intention to avoid false positive conclusions to the extent possible:

". . . the idea that is implicit in the term 'exceptionally well conducted' is that there should be some demonstration of the ability to replicate results, and . . . this stems from the fear of false positives, regulation proceeding on the basis of falsely positive evidence." (Wrenn, Tr. 102)

False positive results must be guarded against, even if the occurrence of such false positives is fairly rare. Dr. Donald Kennedy (Commissioner, FDA) testified that:

". . . we may experience 'false positive' results in some animal bioassays. This possibility cannot be denied, although the weight of scientific evidence collected thus far strongly suggests that such an experience is not the general rule, and may only occur infrequently." (Kennedy, S. 7)

Dr. Kennedy suggested a reason why false positives are rare:

"It just turns out that with most animal studies the results of [experimental] error are more likely to make a substance come clean than to show that it is carcinogenic." (Kennedy, Tr. 571)

Dr. Francis Roe (AIHC) described three reasons why animal bioassays might lead to false positive results:

". . . because of chance . . . because the test agent at high dosage predisposes to a change . . . which, in turn predisposes to cancer . . . because the test agent modified the response of the animal to an agent already within it . . . or to an agent that is currently in its background environment." (Roe, S. 67)

Dr. Roe continued:

". . . When it comes to measuring the false-positive rate for predictive animal carcinogenicity tests, we have no way of doing it . . . [an] alternative is to see whether known human carcinogens produce tumors in laboratory animals. With the exception of arsenic, they do." (Roe, S. 69)

Dr. Arthur Upton (Director, NCI) also mentioned some factors which might lead to the acceptance of false positive results:

"It needs to be emphasized that the NCI bioassays, like any other well-designed cancer test, are interpreted continously and carefully. A chemical is not labelled as a carcinogen automatically if it causes a statistically significant increase in tumors at one site in one species. If an increase is observed, the experiment is reviewed thoroughly, including consideration of the etiology of the tumor type, its occurrence in untreated controls in other experiments, dose-response relationship, etc. Many experiments raise specific problems of interpretation; the resolution of these problems requires evaluation by experienced professionals in several disciplines, and cannot be reduced to a formula." (Upton, S. 12)

During oral testimony, Dr. Upton added that the "adequacy of the pathological evaluation of the lesions" (Upton, Tr. 289) is an additional factor which must be reviewed in order to avoid false positive conclusions.

It is OSHA's intention to subject positive evidence of carcinogenicity to sufficient scrutiny to take account of the confounding factors mentioned above and to rule out certain pitfalls which can lead to falsely positive results, despite the apparent infrequency of such occurrences. Specific steps which will be taken by OSHA to reduce the possibility of false positive results leading to improper regulation are discussed below.

(b) Should OSHA Prescribe Protocols for Design and Execution of Carcinogenesis Bioassays?

A few witnesses representing industry and environmental groups testified that OSHA should define protocols for the design and conduct of animal carcinogenesis bioassays, while the majority of testimony favored no designation of acceptable experimental protocols.

Comments submitted by the Environmental Defense Fund, for example, included the suggestion that ". . . the Secretary should, in the 'cancer policy,' establish standards for [the] conduct [of bioassays] . . . [t]he Secretary should coordinate with any

party carrying out such studies to insure that they met the standards set up . . ." (EDF, S. 9). Mr. Leslie Dach (EDF) suggested that OSHA should base such standarized protocols on material being developed by other agencies:

"(i)n generating these guidelines there are a number of places that OSHA can turn to for guidance, including the guidelines being developed under the Federal Insecticide, Fungicide, and Rodenticide Act, and under the Toxic Substances Act. We would expect the Secretary to take a close look at these and use them as the basis for coming out with standards for studies . . . "(Dach, Tr. 7341)

Two industry witnesses, Dr. Paul Kotin (Johns-Manville) and Dr. Adrianne Rogers (MIT) were much more emphatic in their exhortations that OSHA should prescribe standards for acceptable bioassay procedures. Dr. Kotin said:

". . . (i)f indeed a policy, a regulation, is going to require among other elements of input a body of scientific knowledge . . . this clearly calls for a . . . detailed requirement on the part of the regulatory agency in terms of setting up of standards and guidelines for testing, and something more specific than well-performed tests or extremely well-performed tests, and something more specific than one or two species. There must be some attempt to identify the species and the strains within the species . . . (Kotin, Tr. 8618)

". . . I would recommend that standards and guidelines for testing be evolved and be an integral part of the regulation . . ." (Kotin, Tr. 8619)

Dr. Kotin's suggestion for the way in which OSHA could produce such testing protocols differed from that of Mr. Dach. He testified:

". . . an agency of the Executive—one of the major agencies, departments in the Executive Branch with its resources should have no trouble in convening—and not only find no trouble but naturally, get agreement on the part of a series or a number of acknowledged experts—and let's just assume that somebody in academia has no ax to grind—with no ax to grind who would come up with a series of protocols . . . these people can be gotten together, and this be done." (Kotin, Tr. 8658)

In his written comments, Dr. Kotin stated:

". . . (i)t is indefensible to base regulatory decisions on the use of a non-standardized test for carcinogenic bioassay." (Kotin, S. 21)

Dr. Rogers agreed with Dr. Kotin that OSHA should prescribe bioassay protocols. Dr. Rogers testified:

". . . we believe that proposed OSHA policy is deficient [in] that it does not . . . have clear criteria for published studies which will be considered acceptable as evidence of carcinogenicity in animals . . . or establish protocols to be used for new tests to be conducted in order to provide acceptable evidence . . ." (Rogers, Tr. 6552)

In a joint statement, which Dr. Rogers wrote with Dr. Paul Newberne, these scientists contended that:

". . . The proposed OSHA policy is deficient in that it does not . . . have clear criteria for published studies which will be considered acceptable as evidence of carcinogenacity in animals . . . or establish protocols to be used for any new tests to be conducted in order to provide acceptable evidence . . . [if] regulatory decisions are going to be approached in an explicit, if arbitrary, manner, it is most important to include a complete definition of the quality of the science to be involved, e.g., what scientific tests should be used, how they are going to be run . . ."

* * * * *

". . . [w]e propose that OSHA . . . establish protocols [guidelines], to be used for new studies of test substances . . . the protocols should . . . cover the materials and methods used in all tests including sex, species, source, strain and age of the test animals, diet, water source, housing temperatures, humidity and so forth . . ." (Rogers and Newberne, S. 6, 8)

Dr. Rogers and Dr. Newberne made the following suggestion for how OSHA could produce such standardized test protocols:

". . . [t]he criteria and protocols [guidelines] should be developed in conjunction with a group of scientists knowledgeable in all aspects of chemical carcinogenesis and then submitted to larger groups for review and comments . . ." (Rogers and Newberne, S. 8)

Witnesses who advised OSHA to establish specific acceptable bioassay protocols differed greatly on what such protocols should consist of. The EDF statement made no attempt to specify what acceptable protocols would be, except for the very general statement, made by Mr. Dach:

". . . [t]he goal we have in mind for these standards is to ensure that the work that is submitted to OSHA . . . is done in such a way that it can support a conclusion, positive or negative . . ." (Dach, Tr. 7348)

Dr. Kotin wrote that ". . . the number of factors that can significantly affect animal bioassay data for carcinogenesis are myriad . . ." (S. 20). Among the "myriad" factors listed were very general factors such as "selection protocol for 'test' and control" and such highly specific factors as "cage composition" and "circadian rhythm effect" (Kotin, S. 20). Dr. Kotin's written comments indicating that specific experimental protocols could be produced by an appropriate group of experts, mentioned above, appear to be contradictory to his oral testimony, where he made clear that protocols for testing could not be specified in advance:

". . . I would not want standards and guidelines to be interpreted as a straight jacket, a variety of sets and standards and guidelines would be necessary . . ." (Kotin, Tr. 8619)

Dr. Kotin also stated in oral testimony:

". . . [i]f you are going to ask me for specific experimental protocols here, obviously I am not going to give them to you because the point again I made in my generalization is they would vary . . . having done it in the past, I suppose I could lay it out again but I cannot lay out a series of protocols for you right now." (Kotin, Tr. 8656–8657)

Dr. Rogers' testimony on this point advocated prespecification of bioassay protocols, including such minute details as "water source" and "humidity" in animal rooms. However, when asked "Would you apply these criteria to all animal experiments?", she replied, "Yes. I think most of them. It depends what the purpose of the experiment is. . . ." (Rogers, Tr. 8598.) In response to a further question, "if an experiment did not meet your criteria, would you consider it to be an invalid test . . . would you consider any conclusions drawn from that to be invalid with respect to carcinogenicity?", Dr. Rogers replied: "No. It depends on what the conclusions are that one is going to draw" (Rogers, Tr. 8598).

Other witnesses agreed unanimously that where a Federal agency has authority to conduct bioassays or specify proper procedures for bioassay design and execution, it would be impossible or undesirable to attempt to delineate what such acceptable or minimal protocols would consist of. Dr. David Rall (Director, NIEHS) was asked ". . . is it fair to conclude that you believe that there should be some minimum criteria of experimental design, of conduct and interpretation that have to be met before positive results in animal tests are used as the basis of categorizing a substance as a potential human carcinogen?" (Tr. 390). Dr. Rall replied that he favored "performance guidelines" rather than specific standards for performance of animal bioassays:

"I think . . . it is much better to write performance standards than a by-the-numbers standard, thou shalt have x something or other . . . the scientific community could and probably should draft performance standards for laboratory animal tests . . . these should be rather guidelines than specific. I think you want to talk about what the test will show rather than exactly how you do it . . . so you can . . . allow the flexibility to design the experiment in a way that suits the situation." (Rall, Tr. 390)

Dr. Adrian Gross (FDA) addressed this topic when asked ". . . did I understand you to say that you would not favor the promulgation of rigid guidelines for the conduct of tests?" Dr. Gross replied, "That is correct, yes, sir." In response to the further question, "And did I understand you to say that you think that . . . flexibility in the design of tests would be in the long run a benefit [to] the industry?" Dr. Gross responded: "Of the industry and of all of us as members of the community, yes" (Gross, Tr. 1944–1945). Dr. Gross was earlier asked ". . . you stated that you did not favor rigid standardization of testing, and I think I understand that. Do you not favor a standardization of minimum standards for testing protocols?" Dr. Gross replied:

"No, not really. Beyond certain minimum requirements. For instance . . . one minimum requirement . . . is that the test be a relevant one . . . test something we can deal with, test in a susceptible animal and so on, an informative sort of test. But beyond that, how much testing, how many animals at what levels, how often, this kind of stuff I would say we would be better off not to specify that." (Gross, Tr. 1945–1946)

Dr. Richard Griesemer (NCI) similarly advised OSHA not to attempt to prescribe experimental protocols or establish minimal requirements for acceptable studies:

". . . as a scientist, I believe it undesirable to attempt to standardize protocols or to attempt to come up with a minimum requirement for a carcinogen bioassay . . ." (Griesemer, Tr. 930)

Dr. Griesemer added that the question of standardization of bioassay protocols was under active consideration by international experts:

". . . I am leaving this afternoon for a meeting in Germany where we are planning an international meeting to work specifically on standardization. But there is already an awareness and an assumption that it will not be possible and in fact is not desirable . . . each chemical is different. Each system is different . . ."

* * * * *

"I am concerned with the best possible experiment for the purpose. That does not mean standardized tests . . . I think there is a consensus of opinion about what is a proper experiment after the experiment is over."

* * * * *

". . . [standardized tests] might tend to assure uniformity in the way an experiment is conducted, and I again find that an undesirable approach to research. I think what is required is not uniformity. What is required is the truth." (Griesemer, Tr. 929–930, 932–933, 934)

Dr. William Lijinsky (NCI–FCRC) was asked ". . . are you aware of [an] attempt to come up with one criteria (sic) to be used by everybody in this area of standards for animal bioassays?" Dr. Lijinsky replied:

"I do not know of any attempt to get a single set of criteria. I am not sure it is possible, because chemicals vary so much . . ." (Lijinsky, Tr. 1040)

Dr. Bernard Weinstein (Columbia Univ.) testified:

". . . I think it would be wrong to insist, for example, that the document state that x number of animals should be used and x number of species should be used, and x number of dosages should be used, and x number of histologic sections should be taken and so forth because . . . this is an evolving field . . . the NCI bioassay . . . is under surveillance . . . so I do not think we need specify or can specify at the present time these details.

". . . the subject is just too complex to spell out procedures that are appropriate for testing a broad range of compounds. This has to be taken on a compound-by-compound basis . . . no one can spell out at the present time as to what should be done in terms of the best carcinogen assay. It is just too complicated and it will vary under different conditions." (Weinstein, Tr. 2257, 2260)

Additional scientists noted that the field of bioassay testing is an active one and protocols are constantly being refined. Dr. Arthur Upton (Director, NCI) pointed out that ". . . the design of the NCI bioassay has been progressively improved over the years, to incorporate new knowledge . . ." (Upton, S. 10). Dr. David Groth (NIOSH) testified, ". . . it would be inadvisable to put in a rigid set of criteria and then have to change this every year as we learn more information . . ." (Tr. 2890). Dr. William Lijinsky (NCI–FCRC) added, ". . . [t]hese standards, the laboratory procedures, are continually changing, but there are minimal (NCI) standards" (Tr. 1031).

Mr. Grover C. Wrenn, Jr. (OSHA) testified at the outset of the hearing that ". . . we don't envision publishing detailed criteria for the design and conduct of studies . . . in much greater detail than is suggested in the preamble to this proposal . . ." (Tr. 103) ". . . the proposal does at least set forth some criteria which imply the kinds of protocols that are appropriate for animal experimentation in the assessment of carcinogenic potential . . ." (Tr. 227). When Mr. Wrenn was asked: ". . . [the proposal] doesn't say what criteria must be present or what circumstances must be present in a particular study in order to qualify it . . . do I understand then that in not putting such criteria into the proposed standard, that OSHA found it impossible to develop such criteria as of October of 1977?", he replied, "I am not sure that would fully explain the absence of those criteria in the proposal. There is also the possible benefit of that measure of flexibility within the future operation of this policy . . ." (Tr. 228).

OSHA finds that in light of the Record established in this proceeding, it is neither advisable nor possible to set particular experimental protocols for all acceptable carcinogenicity bioassays. The test protocols of scientific institutions are constantly being changed as new knowledge is gained, which makes specification of protocols impractical. There appears to be nearly unanimous agreement that competent scientific experts can distinguish between acceptable and unacceptable bioassay protocols. If OSHA finds that particular studies are of doubtful validity because of flaws in experimental design and/or execution, such studies will not be utilized as the basis for regulation.

(c) Should OSHA Prescribe Standards for Interpretation of Bioassay Data?

As discussed above, OSHA will review experiments of varying experimental designs and experimental protocols to decide whether there is sufficient indication of carcinogenic activity to regulate exposure to the substance under consideration. OSHA's position, clearly indicated in the proposed regulation and now supported by substantial evidence in the Record, is that such interpretation of experimental results will be done by scientific experts and may involve scientific review. A few witnesses argued, however, that the proposal for expert scientific review of experimental results is too broad and needs to be defined by specific interpretative protocols and procedures for assessment of bioassay data. For example, some of the many reasons why it should be impossible to devise a standardized method of interpreting bioassay data were pointed out by Dr. Leon Golberg (CIIT):

"The . . . issue concerns the evaluation of toxicity data . . . the complexity of the confounding issues of which we are now aware, the plethora of procedures being applied nowadays . . . make it imperative to involve a group of the most knowledgeable and experienced experts . . . it is essential to treat each compound as a unique entity . . ." (Golberg. Tr. 6485–6487)

During oral testimony, Dr. Golberg reiterated the need for flexibility, rather than rigidity, in interpreting results:

". . . we have a record of hundreds of tests that have been carried out in the recent past . . . which could not really be assessed adequately by . . . rigid criteria . . ." (Golberg, Tr. 6499).

Dr. Roe (AIHC) also stated:

". . . the task of distinguishing between . . . valid and relevant tests and . . . invalid and irrelevant tests is not one that can be delegated to a computer. For this purpose, there is no better way than to rely on the collective judgment of a group of independent, relevantly experienced and well-informed scientists . . ." (Roe, S. 59)

Mr. Leslie Dach (EDF), who had advocated standardization of bioassay protocols (see above), stated that such standardization should not be extended to interpretation of results:

". . . evaluation will be done by the [Labor] Department on the basis of looking at the data—there are many cases where the author of a paper reaches a conclusion which is not agreed to by other independent reviewers or readers—the standards we had in mind would apply to the conduct of the experiment and not its interpretation." (Dach, Tr. 7348)

Many witnesses unanimously agreed that interpretation of bioassays should not be done in a standardized manner, but rather by reliance on scientific judgment of experts in the field of carcinogenesis testing. Dr. David Rall (Director, NIEHS) testified:

. . . the recommendation of a scientist would be . . . to apply as much scientific judgment to each case as is compatible with legal and regulatory requirements. (Rall, S. 14)

Dr. Arthur Upton (Director, NCI) stated:

". . . the NCI bioassays, like any other well-designed cancer test, are interpreted continuously and carefully . . . many experiments raise specific problems in interpretation; the resolution of these problems requires evaluation by experienced professionals in several disciplines, and cannot be reduced to a formula." (Upton, S. 12)

Upon cross-examination, Dr. Upton reiterated:

"[a]ll these questions [of interpretation] go into the evaluation of a test result, and I suppose that if one wanted to write a book of pathology, one could characterize this process. But to reduce it to a simple formula would be very difficult." (Upton, Tr. 289)

Additional scientists advising OSHA not to attempt to specify formulae for the interpretation of bioassay results included NIOSH, which said:

". . . the studies will be validated by scientists of repute or an advisory committee. Therefore, there is no need to write in obvious criteria . . . to suggest that these criteria should be written into the document is excessive material. I think it is a waste of paper." (NIOSH, Tr. 3005–3006)

Dr. Richard Griesemer (NCI) wrote:

". . . the criteria for judging the carcinogenicity of a substance cannot be reduced to a formula. They require the exercise of good scientific judgment as well as good experimentation." (Griesemer, S. 11)

During oral testimony, Dr. Griesemer testified:

". . . there are a number of possible conditions under which the evidence might be judged as sufficient . . . when we interpret [bioassay results], we may not be able to decide whether a chemical is carcinogenic on the basis of that data . . . that is why when we analyze the results of experiments we start by analyzing the adequacy of the experiment itself. If it is insufficient we do not go any further. We ask industry or whoever conducted that experiment to do it over." (Griesemer, Tr. 930–931, 932, see also Tr. 934)

Support for the concept that it is possible and/or desirable for OSHA to specify procedures for interpreting results of carcinogenesis bioassays was generally limited to testimony presented by Dr. Paul Kotin (Johns-Manville) and Dr. Adrianne Rogers (MIT) and the joint statement written by Drs. Rogers and Paul Newberne (MIT). As described above, industry witnesses Golberg and Roe specifically rejected the notion that data interpretation could be done by a prescribed protocol. In contrast, Dr. Kotin testified, ". . . standards and guidelines for data interpretation are necessary (Kotin, Tr. 8619) . . . it is imperative that . . . some form of evaluation be introduced into the regulatory procedure . . . (Tr. 4895) . . . [the proposal] fails to provide a mechanism . . . with guidelines for experimental protocol development, implementation, data analysis and interpretation, and this indeed is where a generic approach is vitally needed . . ." (Tr. 4895). Dr. Kotin's testimony, however, contains several statements which appear to contradict the notion that OSHA should set interpretative standards. For example, Dr. Kotin, as quoted above, continued, ". . . a generic approach (to data analysis) is vitally needed, not that a single test is valid for everything . . ." (Tr. 4895).

In their joint statement, Drs. Newberne and Rogers wrote:

"The proposed OSHA policy is deficient in that it does not establish clear criteria for published studies which will be considered acceptable as evidence of carcinogenicity in animals . . . tests which rely on [mouse liver] lesions, without adequate control populations, confirmation by histologic diagnoses, observation of biological behavior and other available methods, are of limited usefulness as a basis for regulatory decisions. Proper standards of acceptability of data or test protocols should recognize and provide for these factors in advance".

* * * * *

". . . the proposed regulation as now written appears to allow acceptance of studies which do not conform to currently recommended protocols".

* * * * *

". . . we propose that OSHA establish clear criteria for published studies which will be considered acceptable as evidence of carcinogenicity of a test substance." (Newberne and Rogers, S. 6, 7, 8)

Drs. Rogers and Newberne also stated:

"[e]stablishing the scientific criteria on an ad hoc, after the fact basis is highly unsatisfactory from a scientific point of view, and we would assume the same is also true from a regulatory point of view.

* * * * *

"[t]he potential effects of this failure to provide standards of acceptability of scientific evidence are well illustrated by experience . . ." (Newberne and Rogers, S. 8, 6)

Dr. Newberne and Dr. Rogers also offered specific suggestions for factors which should be taken into account in data interpretation:

"[m]any studies . . . were designed for purposes other than testing its carcinogenicity and therefore may not have included adequate numbers of animals, proper control animals, control and monitoring of environmental conditions including diet, assay of compound purity, or other requirements . . .

* * * * *

"The protocols should, *inter alia*, cover the materials and methods used in all tests including sex, species, source, strain and age of the test animals, diet, water source, housing temperature, humidity and so forth so that tests can be exactly replicated . . ." (Newberne and Rogers, S. 7, 8)

A third list of suggested factors which interpretative protocols might include was offered in Dr. Rogers' individual statement. Dr. Rogers wrote:

"An acceptable protocol must be designed specifically for the purpose of investigating the carcinogenicity of the agent in question . . . [f]oremost among the elements of a properly designed study is the condition that the only variable is exposure to the test agent . . . this requires the use of control animals . . . as well as careful, systematic monitoring of the animals . . . all test animals should be examined grossly and microscopically for evidence of tumors . . . there should be a complete and accurate autopsy of each animal. . . . tests of statistical significance must be applied. . . . studies should. . . . contain a full description of all the materials, methods . . ." (Rogers, S. 4–6)

Dr. Rogers warned:

"Any regulation which permits the reliance on studies which fail to meet these or similar criteria will allow and encourage poor scientific practices, and . . . the possibility of significant regulatory error . . ." (Rogers, S. 6)

During oral testimony, Dr. Rogers stated:

". . . we believe that the proposed OSHA policy is deficient and that it does not establish clear criteria for published studies which will be considered acceptable as evidence of carcinogenicity in animals . . . (Rogers, Tr. 6552)

". . . the proposed regulation does not adequately specify criteria for evaluating animal data which will be used to determine whether a substance is carcinogenic. . . ." (Rogers, Tr. 8565)

Dr. Rogers advocated concepts such as "a basic and common sense approach" (Tr. 8601) to data interpretation and stated:

". . . I think the tests that have been done should be evaluated using very careful scientific criteria, and then obviously it comes to a decision . . ." (Tr. 8605)

Dr. Rogers also stated:

". . . the proposed regulation should include provisions which to the extent possible assure that regulatory decisions which use it as a framework are based on sound, relevant data . . ." (Rogers, Tr. 8565)

In saying that such provisions should be established "to the extent possible," Dr. Rogers' testimony was in agreement with that of three other witnesses: Dr. Donald Kennedy (Commissioner, FDA), Dr. Richard Bates (FDA/NIEHS) and Mr. Grover C. Wrenn, Jr. (OSHA). Dr. Kennedy testified that standards such as those involved in interpreting bioassay data be described and published "wherever possible" (Kennedy, Tr. 523). Dr. Bates said, ". . . I do favor [adopting interpretative criteria] to the extent that it is feasible . . ." (Bates, Tr. 597). Mr. Wrenn was asked (by Mr. Newman): "And you are saying . . . if I understand you correctly, that it would be desirable to the extent possible to set forth in this standard in its final form such criteria [to qualify a study]?" Mr. Wrenn replied, "To the extent this record permits doing that, yes" (Wrenn, Tr. 228). He then added ". . . we have no prejudice against including criteria of that sort within the final standard" (Wrenn, Tr. 229). Earlier in his oral testimony, Mr. Wrenn made the point that "[OSHA] will rely to some degree upon the evidence we get in this proceeding to clarify . . . what you rely upon to determine whether a study is well conducted or not" (Wrenn, Tr. 103).

It is clear from a review of the record that with the exception of Dr. Rogers and, to some extent, Dr. Kotin, scientists testified that it would be unwise and futile for OSHA to attempt to specify criteria and standards for acceptance of bioassay results. As discussed below, some of the criteria which were suggested by Dr. Rogers, such as consideration of control animals and availability of a description of experimental procedures, will indeed be among the many factors which OSHA experts will take into account in an evaluation of bioassay data. Specified standards for such criteria will not be promulgated by OSHA, as recommended by witnesses at the hearing.

(d) What Factors Need To Be Taken Into Account by OSHA in the Interpretation and Evaluation of Animal Carcinogenicity Experiments?

As discussed above, a clear preponderance of witnesses appearing at the public hearing did not favor prespecification of factors and standards for acceptable animal bioassay results. OSHA concurs. However, many experts testified on the importance of particular points which should or must be taken into account in determining the reliability of bioassay results. In addition, several reports were submitted into evidence on efforts of previous scientific groups to consider the problem of minimal and/or desirable standards for acceptable animal bioassays and their interpretation:

1. International Agency for Research on Cancer. 1978. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man;

2. Food Safety Council. 1978. Proposed System for Food Safety Assessment;

3. Environmental Protection Agency. 1978. Proposed guidelines for registering pesticides in the U.S., Hazard evaluation: Humans and domestic animals;

4. World Health Organization. 1974. Assessment of the Carcinogenicity and Mutagenicity of Chemicals;

5. National Cancer Institute. 1976. Guidelines for Carcinogen Bioassay in Small Rodents;

6. Health and Welfare Canada. 1973. The Testing of Chemicals for Carcinogenicity, Mutagenicity and Teratogenicity;

7. International Union Against Cancer. 1969. Carcinogenicity Testing;

8. Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation. 1971. Panel on carcinogenesis report on cancer testing in the safety evaluation of food additives and pesticides;

9. Mark Commission. 1969. Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health;

10. National Academy of Sciences. 1975. Principles for Evaluating Chemicals in the Environment.

In addition to these reports, several witnesses submitted statements on criteria for experimental design and data interpretation:

a. American Industrial Health Council. AIHC Recommended Alternatives to OSHA's Generic Carcinogen Proposal;

b. American Petroleum Institute. An Approach to Generic Rulemaking for Regulation of Occupational and Environmental Carcinogens (Hearing Exhibit 252, Appendix C);

c. Hooker Chemical Company. (Hearing Exhibit 71).

Specific suggestions for experimental and interpretative factors are discussed below.

The most important consideration in judging the validity of animal bioassay results is whether the results are taken to support positive or negative conclusions of carcinogenicity of a substance. As discussed above, OSHA's concern is to protect employed persons from exposure to substances for which there is positive evidence of carcinogenicity. Since animal bioassays are generally rather insensitive measures of the carcinogenicity of a substance, criteria for acceptability of positive results need be far less stringent than criteria for acceptability of negative results or evidence of safety. Dr. David Groth (NIOSH) testified on the differences in judging reliability of negative bioassay results as opposed to positive results: "The relative importance of the [adequacy] criteria . . . does depend upon the results of the experiment . . ." (Tr. 2998–2999). The same point was made during the oral testimony of Dr. Samuel Epstein (Univ. of Illinois). Mr. Barnard (AIHC) asked: ". . . I take it then that you would not be willing to accept a negative study that used just 20 animals and were fed 18 months . . . [a]nd yet, you refer to the Innes study by Litton Bionetics where these tests were conducted, as I understand it, for 18 months on 20 animals." Dr. Epstein replied: "Your question is entirely different. Your question asked me would I be satisfied with a negative. The inferences I have made from the Innes study related to positives" (Tr. 1242). This point was stressed by Dr. Donald Kennedy (FDA) (Kennedy, Tr. 571), who pointed out that flaws in experimental design are much more likely to result in false negatives than in false positives. For this reason, interpretative criteria for studies which are positive need to be much less stringent than those which are considered negative. Dr. Kennedy summarized his view on this topic by stating, ". . . there is a real rationale for taking positive results more seriously than negative results." Dr. David Rall (Director, NIEHS) concurred with this view in stating:

". . . there are cases where a single well-conducted experiment giving clearly positive results should suffice to establish a chemical as a carcinogen and to justify stringent

measures to reduce occupational exposure." (Rall, S. 13–14)

Dr. Robert Squire (Johns Hopkins Univ.) also indicated that while there are many pitfalls in execution of bioassays, "*any* clearly positive animal study must be considered as the best qualitative experimental evidence available for human carcinogenic risk" (Squire, S. 13, emphasis added).

This important distinction between negative and positive bioassay data was not clearly made by industry witnesses or briefwriters who called for specific guidelines and protocols without consideration that such guidelines are much more acceptable in an evaluation of the adequacy of negative bioassay data than for positive results.

Another important distinction which was confused in the comments of many witnesses and participants was between defects in design of bioassays and defects in their conduct. If a bioassay is conducted with too few animals, with too low a dose, or for too short a period, this will generally invalidate a negative result, although a clear positive result will nevertheless be valid and meaningful. On the other hand, if an experiment is inadequately conducted or inadequately reported, it may be impossible to draw any valid conclusions, positive or negative, however good the experimental design. Many of the comments about the interpretation of "inadequate" tests failed to make the distinction between these two categories of inadequacy.

It is important to emphasize that "negative" results in carcinogenicity bioassays simply define a limit beyond which carcinogenic activity would have been detected. Absolute safety can never be demonstrated; agencies concerned with establishing safety standards must balance the relative insensitivity of animal bioassays with the high cost of such tests and the increasing chances of experimental error as the experiment becomes larger and more elaborate. If the results of animal bioassays appear to support a conclusion of lack of carcinogenicity, OSHA's interest in reviewing experimental protocols is limited to the possibility that a more extensive examination of pathological or other criteria may possibly lead to the conclusion that the compound was in fact positive for carcinogenicity. If the available evidence indicates that the chemical is not positive for carcinogenicity, OSHA's position on that particular chemical is the same as if the chemical had never been tested for carcinogenicity.

Several expert witnesses presented opinions on specific factors in design and execution of animal carcinogenicity bioassays which may be important in judging adequacy and reliability of results. Such suggestions involved several specific areas which are discussed below.

Controls. Most witnesses agreed that control or untreated animals are essential to any experimental determination of carcinogenicity. Few witnesses, however, suggested that OSHA set minimal or desirable standards for what constitutes an adequate control group. The importance of adequate controls was emphasized by Dr. Walter Heston (NIH), who wrote,

"The only difference between the test group and the controls should be that the test group receive the candidate substance while the control animals are free of the candidate substance. In this way any difference between the two groups in incidence of hepatomas or other tumors can be attributed to the substance tested. While it is true that the incidence of induced or spontaneous tumors can be changed by environmental influences, induced changes in tumor incidence are not difficult to determine accurately if the environmental and genetic factors are properly controlled. In other words, properly controlled carcinogenesis bioassays in mice give reliable and meaningful results." (Heston, Post-Hearing Comment, pp. 15–16)

Dr. Ralph Yodaiken (NIOSH) agreed: "It would be unthinkable . . . to have a study without controls . . ." (Tr. 3005). Dr. David Groth (NIOSH) added, ". . . in the field of science, the requirements for experiments and testing a single chemical or agent are that the control and exposed populations are different only with respect to one variable . . ." (Tr. 2991–2992). Mr. Newman asked the NIOSH panel, ". . . (y)ou would say, then, that part of your minimal criteria for the acceptance of animal studies would be that there is a control population used, would you not?" Dr. Yodaiken replied, "Yes" (Tr. 2992). ". . . the most important thing . . . is that . . . the control and exposed groups must be similar except for the one major variable, so that they [can] compare the exposed with the control group" (Tr. 2997).

Dr. Rogers concurred:

". . . foremost among the elements of a properly defined study is the condition that the only variable is exposure to the test agent . . . this requires the use of control animals . . ." (Rogers, S. 4)

Dr. Arthur Upton (Director, NCI) mentioned that the evaluation of bioassay results may take historical controls into account:

". . . the experiment is reviewed thoroughly, including consideration of . . . occurrence [of tumors] in untreated controls in other experiments . . ." (Upton, S. 12)

As is discussed further below, historical controls may be especially important in evaluations of positive bioassay results.

Number of animals in the bioassay. Acceptable positive results can be based on small numbers of animals. This was emphasized by many witnesses. Dr. Harold Stewart (NIH) related how the carcinogenicity of estrogen was discovered in a small-scale experiment:

"Professor Lacassagne demonstrated the carcinogenicity of estrogen. He used five male mice and got cancer of the breast in all five . . . [i]f you have breast cancer in five male mice it has got to be a carcinogen . . ." (Stewart, Tr. 489)

Dr. William Lijinsky (NCI–FCRC) agreed that "five males with breast tumors is an extraordinarily large number . . ." (Tr. 1074)

Dr. Richard Griesemer (NCI) said:

". . . if ten animals are exposed to a chemical and all ten of them develop stomach tumors in six months, one does not need much more information to draw a conclusion. If, however, the same experiment were conducted and no tumors were produced in excess of those in the controls, one would say that was an inadequate experiment." (Griesemer, Tr. 933)

This comment provides another illustration of the distinction between the requirements for demonstrating positive and negative results.

Dr. David Rall (Director, NIEHS) indicated that in some cases, only a few animals can suffice for a clear bioassay result: ". . . if the chemical is a hot carcinogen, you do not need as many animals as if it is not . . ." (Rall, Tr. 442)

Another case where a positive conclusion of carcinogenicity was based on a small group of animals was cited by Dr. Ralph Yodaiken (NIOSH), who testified:

"If a study comes in where only ten animals have been used for a variety of doses, as was the case with the Dow Chemical study on acrylonitrile, it was the professional judgment of the people at NIOSH that this was a valid [positive] study . . ." (Yodaiken, Tr. 2991)

Mr. Edward Baier (NIOSH) concurred: ". . . it might very well be that a few animals can indicate enough or supply enough data to draw a conclusion . . ." (Baier, Tr. 3003)

The relevance of the number of experimental and/or control animals must be judged in the context of the particular experiment under

consideration. Dr. David Groth (NIOSH) was asked ". . . it might very well be that a few animals can indicate enough or supply enough data to draw a conclusion. Is this correct?" "On the other hand, you can have several hundreds of animals and not be able to draw a conclusion. Is that correct?" Each time, Dr. Groth replied, "Yes" (Tr. 3004).

Other witnesses, including Drs. Renate Kimbrough (CDC) and Samuel Epstein (Univ. of Illinois), mentioned that the number of animals in a bioassay was an important consideration in negative studies. As Dr. Umberto Saffiotti (NCI) said, ". . . the detectability is largely a function of the magnitude of the experimental group . . ." (Saffiotti, Tr. 855). The only witness who said that the magnitude of experimental and/or control groups was relevant to both negative and positive carcinogenicity bioassays was Dr. Rogers, who said that tests of statistical significance must be utilized in the interpretation of bioassay results (see below) and that "usually at least 50 exposed and 50 controls" were required for statistical tests (Rogers, S. 6). However, Dr. Rogers said during oral testimony, "The numbers of animals to be used really is governed by what levels of statistical significance one wants . . ." (Rogers, Tr. 8598).

Duration of dosing. Duration of dosing in carcinogenicity bioassays is another criterion which should be specified if one is setting minimal standards for negative studies (Epstein, Tr. 1238; Epstein, S. 94; Weinstein, Tr. 2249), but which need not be so specified if positive results are revealed. As Dr. Leon Golberg (CIIT) testified,

". . . two complete years have not passed in any of the [Chemical Industry Institute of Toxicology] tests, but we have carried out interim sacrifices . . . and some of these are already yielding very suggestive results . . . we are studying aniline, and at the first sacrifice of the animals exposed to aniline hydrochloride we found a . . . fibroplasia of the splenic capsule . . . taken in conjunction with a study . . . released by the National Cancer Institute . . . where they observed tumors of the spleen derived from connective tissue, this is a very close link which suggests that what we are observing are early stages of what will ultimately develop into the same kinds of tumors." (Golberg, Tr. 6505–6506)

Dr. Richard Griesemer (NCI) similarly testified that positive results can be obtained after relatively short periods of dosing:

". . . we know of experiments where there was only a single exposure and cancers [were] produced. We know of cancers that are induced in very short periods . . . three azo dyes [produced] liver cancers in 90 days. I would say that is very short." (Griesemer, Tr. 1001)

Autopsy and pathology procedures. This is another area where specifications can be made for negative studies but which must be considered in the context of particular positive studies. As Dr. Golberg testified:

"I can give you the case of dinitrotoluene . . . in our tests to date . . . the histology has not been done, but the gross findings at autopsy suggest that there is liver cancer in these animals . . ." (Golberg, 6506)

Dr. David Groth of NIOSH testified that ". . . the animals should be autopsied and tissues examined for the lesions, including cancer" (NIOSH, Tr. 2889). Dr. Arthur Upton (Director, NCI) agreed that accurate pathological diagnoses are essential in making a positive determination from a carcinogenicity bioassay:

". . . a significant or conclusive effect in a test species . . . involves an assessment of the adequacy of the pathological evaluation of the lesions, were they in fact tumors or were they misdiagnosed, were they simply abcesses or inflammatory lesions?" (Upton, Tr. 289)

Dr. Weinstein called for "clear histologic verification that the lesions were malignant neoplasms . . ." (Weinstein, Tr. 2254–2255)

Monitoring of animal health. Several witnesses mentioned that factors in the design of experiments which involve surveillance of the animals, including their weight and food consumption, could be relevant to the outcome of animal bioassays. Dr. Epstein mentioned that "diet and care" of animals, if poor, can make carcinogenicity bioassays insensitive (Epstein, S. 94). Dr. Kimbrough said that "what the animal weights were" would influence her judgment of the adequacy of a study (Kimbrough, Tr. 1796). Dr. William Lijinsky (NCI–FCRC) indicated that monitoring of animal health and food intake was important in the conduct of bioassays under his direction (Lijinsky, Tr. 1032–1033, 1035–1036).

Despite these concerns, only one witness, Dr. Adrianne Rogers (MIT) called for OSHA to establish specific "minimum criteria . . . which would indicate . . . systematic monitoring of and control over all the animals . . ." (Rogers, Tr. 8565). Dr. Leon Golberg (CIIT) stated that ". . . [n]o arbitrary rule of the thumb is available . . . [for] how to select the upper dose in a long-term toxicity test . . ." (Golberg, S. 3). When Dr. Golberg was asked: "Would you consider a very serious weight loss (to be) more than 10 percent of the animal's weight?", Dr. Golberg replied:

". . . I do not think that by itself would vitiate the total outcome of the test and its interpretation." (Golberg, Tr. 6526–6527)

Monitoring of animal diets and compound purity. Several witnesses voiced concern about the possibility of false positive results which might be caused by contaminant substances. The related question of false negative results occurring by contamination of control diets with carcinogens was also discussed. Dr. Golberg alleged that:

". . . it [is] very rare . . . for anyone to say, well, why wasn't this compound adequately characterized? Why wasn't the dietary level of this material checked, as it would be required under good laboratory practice" . . . (Golberg, Tr. 6522).

Dr. Richard Niemeier (NIOSH) said ". . . probably the feed should be monitored periodically for [a] particular contaminant" (Niemeier, Tr. 2994). Dr. Adrianne Rogers (MIT) called for "systematic monitoring of . . . diets, exposures . . ." (Rogers, Tr. 8565) for bioassays to be acceptable. Among other "standards for acceptable studies" Dr. Rogers included "assay of compound purity" (Rogers, S. 7).

This issue has several aspects which were not always clearly distinguished in testimony and comments:

1. Monitoring of actual (as opposed to nominal) levels of a chemical in a test diet is desirable primarily in cases where the exact intensity of exposure is in question—e.g., if a quantitative risk extrapolation is to be made. There is no obvious way in which failure to measure dietary levels would invalidate the qualitative results of a test that gave a positive result, and no showing was made that it would do so.

2. The presence of potentially carcinogenic impurities or contaminants is of importance primarily when a technical product is tested. In such cases, it is possible for the technical product to be carcinogenic even though the pure chemical may be inactive. However, since workers are exposed to the technical product, it is unlikely that testing in these circumstances will give rise to false positive results. Of more concern in general is the likelihood of obtaining false negative results by testing the pure chemical.

3. Contamination of control diets with carcinogens is in general likely to give rise to false negative results, by increasing the tumor incidence in the control groups.

4. The most difficult issue is raised by the circumstance in which a change in a manufacturing process or in formulation has led to the elimination of a potentially carcinogenic contaminant. In this hypothetical circumstance, a

positive result obtained in the past may be irrelevant to the inference of risk from the currently manufactured technical product. Although no cases of this kind were demonstrated or even plausibly suggested in the hearing Record, OSHA is cognizant of the theoretical possibility that they may arise in the future. If satisfactory evidence is presented that a positive result obtained in the past was attributable to a contaminant, OSHA will review such evidence in detail. It would appear that several areas of concern in that regard would be the following:

(a) demonstration that the currently-manufactured product is not carcinogenic, in a test at least as sensitive as the earlier test which gave a positive result;

(b) plausible evidence that the product used in the earlier test contained a carcinogenic contaminant;

(c) demonstration that the mixture of this contaminant and the currently manufactured product yields positive results similar to those obtained in the earlier test.

OSHA recognizes that these criteria are stringent, but believes that it would be the Agency's responsibility to apply stringent standards of proof before discounting the results of a positive test. OSHA can in no circumstances discount a clear positive result as the basis of hypothesis or conjecture, but will require detailed verification that a disputed postive result can be replicated by re-introducing the hypothetical active agent.

In addition to these factors which are important in judging the adequacy of the design and execution of bioassays, a number of witnesses discussed factors which should be taken into account in their interpretation. These factors included assessment of statistical significance, dose-relatedness of carcinogenic activity, reproducibility of results, and description of experimental procedures and results. These are discussed below.

Statistical significance of results. As mentioned above, all experiments should generally include a control group in order to make conclusions of any kind justifiable, even though, in some cases, the control group may be simply historical or based on scientific experience with the particular colony or strain of test animal. Where an obviously positive result is not observed, a more sophisticated presentation of control versus treated results is needed and statistical significance is necessary to demonstrate that the incidence of tumors in experimental animals was indeed causally increased by exposure to the test agent.

No clear formula for how to determine whether a particular set of results is statistically significant emerged from the hearing. Certain specific suggestions were made, including that of Mr. Richard Peto (Univ. of Oxford):

"Because in most experiments animals of both sexes and of more than one strain are studied, and the separate incidence of tumours at each of a dozen or more anatomical sites is independently documented, some of the many significance levels calculated will probably be less than 0.05 just by chance. Because of this, individual P-values of 0.05 (or even 0.01) are not necessarily convincing unless the effects concerned can be reproduced in independent experiments or unless the agents concerned show striking activity in a battery of short-term tests; for a single animal experiment to be convincing without such support, a P-value of well under 0.01 (perhaps even 0.001) should usually be required. Unless this policy of requiring rather extreme P-values is adopted, an unacceptably large number of misleading results will emerge by chance alone." (Peto, S. 17)

Another specific suggestion raised was that of Dr. Carroll Weil (Carnegie-Mellon), who offered:

"Statistical tests for significance are valid only on the experimental units (e.g., either litters or individuals) that have been mathematically randomized among the dosed and concurrent control groups." (Weil, S. 2)

Several witnesses testified that it would be undesirable to attempt to predesignate statistical treatment of data or even to specify particular regulatory responses to various levels of statistical significance. As Dr. David Rall (Director, NIEHS) testified:

". . . Clearly if [the experiment] is statistically significant . . . it is a positive experiment and should be treated as such . . . but it seems to me quite clear that there are certain rare tumors in animals, and if after exposure to a chemical you have an increase in those tumors, you ought to be extraordinarily suspicious of that chemical, even though it does not quite hit the magic five per cent." (Rall, Tr. 387–388)

Dr. Upton, on the other hand, warned against acceptance of apparently positive results, even if those results met criteria of statistical significance:

"A chemical is not labeled as a carcinogen automatically if it causes a statistically significant increase in tumors at one site in one species. If an increase is observed, the experiment is reviewed thoroughly . . ." (Upton, S. 12)

Dr. Donald Kennedy (Commissioner, FDA) testified that he would require statistical significance before he would judge the results of a particular bioassay positive (Tr. 563). Upon further questioning, however, Dr. Kennedy added:

". . . I see within the universe of animal testing enough variation in the kinds of experiments done, and thereby in the confidence limits and levels of statistical significance that one would want to assume, that I am not sure that such a prescription wouldn't prove to be more confining than it is helpful." (Kennedy, Tr. 564)

Other testimony supported the view that statistical significance must be evaluated on a case-by-case basis before conclusions or interpretations can be drawn. Dr. Richard Griesemer (NCI) testified that under certain circumstances, the appearance of tumors in "marginally statistical numbers" would still lead to suspicion of the test substance (S. 11). Dr. David Groth (NIOSH) made the important point that evaluations of statistical significance are "particularly important in the case of negative results" (Groth, Tr. 2995), as opposed to the cases of positive results upon which OSHA is charged to react. Dr. Umberto Saffiotti (NCI) discussed the issue as follows:

"[t]here is no specification [in the OSHA proposal] about levels of statistical significance, clearly because these are subsumed in the strong requirement implied by a recognition of causality. As I said above, there is more to a judgment of causation than a strictly numerical value: the latter is but a framework for a complex diagnostic scientific evaluation." (Saffiotti, S. 25)

Further discussion of this issue is presented above in Section V.D. The consensus of the expert opinion presented at the hearing was that, although tests of statistical significance are always desirable, it would be unwise to prescribe rigid criteria for the conduct of such tests, or for the levels of probability to be judged significant.

Dose-relatedness of results. Several witnesses indicated that dose-relatedness of bioassay results could have a bearing on the interpretation of particular experiments. Dr. Arthur Upton (Director, NCI) said that "dose-response relationship" is among the factors involved in interpretation of a bioassay (Upton, S. 12). Dr. Richard Griesemer (NCI) mentioned that "when more tumors form at lower than at high doses" evidence for carcinogenicity was weaker, but under certain circumstances, he "would still be suspicious . . ." (Griesemer, S. 11). Dr. Griesemer also mentioned that "dose relationships" were among factors "not considered as relating to the weight of the evidence for carcinogenicity" at certain meetings of world experts on carcinogenicity (Griesemer, Tr. 931).

Several witnesses warned against any rigid requirements for dose-relatedness

in judging positive evidence of carcinogenicity. Dr. David Rall (Director, NIEHS) pointed out:

"Dose response can be very misleading, often at the very high dose, because the animals are sick; the dose is higher than it ought to be. You see fewer tumors than at a lower dose.

So one would say, 'Well, gee, the dose response is backward,' but actually that really would make sense. So I think it is a little hard to make a categorical statement about that." (Rall, Tr. 389)

Dr. William Lijinsky (NCI-FCRC) stated, ". . . it is not necessary to show a dose response to establish that the compound is a carcinogen . . . it is helpful if there is a dose response; it is not necessary". (Lijinsky, Tr. 1079). Dr. Leon Golberg (CIIT) wrote that at least "three . . . dose levels" be used in experiments where quantitative conclusions of carcinogenic potency were to be drawn; he did not comment on the need for multiple dose levels or dose-relatedness for qualitative determinations of carcinogenicity (Golberg, S. 6).

Reproducibility of results. Several witnesses mentioned that if a compound is shown to be carcinogenic on more than one occasion, this adds a great deal of weight to the conclusion that the compound is a carcinogen. However, these witnesses did not say that replication should be an essential factor in establishing that a compound is a carcinogen for regulatory purposes. Dr. Umberto Saffiotti (NCI) said that "concurrence and reproducibility of the observations are important elements for this assessment [of causality]" (Saffiotti, S. 7). Dr. Bernard Weinstein (Columbia Univ.) said that ". . . in the area of carcinogen bioassay many of us feel that one needs reproducibility . . ." (Weinstein, Tr. 2249). Dr. Weinstein added that such evidence of reproducibility could take several forms, including ". . . adequate numbers of control groups or evidence of different dose levels or different species . . ." (Tr. 2249), while Mr. Grover Wrenn (OSHA) stated that:

". . . the idea that is implicit in the term 'exceptionally well conducted' is that there should be some demonstration of the ability to replicate results" . . . (Wrenn, Tr. 102)

It is important to note that these and other witnesses used the word reproducibility to refer to the *ability* to reproduce results; they did not equate it with the actual reproduction or replication of results. The need for replication of results is discussed in more detail in Section V.D.9. above.

Description of experimental procedures and results. Dr. Adrianne Rogers (MIT) called for "certain minimum criteria" for "description of materials, methods, controls, [and] analytical procedures used . . . to assure that regulatory decisions . . . are based on sound, relevant data . . ." (Rogers, Tr. 8565). Dr. David Groth (NIOSH) agreed that "[t]here should be a sufficient description . . . particularly in the case where you have negative results . . ." (Groth, Tr. 2998). Several witnesses agreed that problems of interpretation of positive studies could be solved by additional data on materials and methods which could usually be readily obtained from the author or laboratory where the study was conducted. Although it is obvious that adequate description of a study is a prerequisite for its correct interpretation, it would be impossible to specify precise minimum criteria for acceptability without arbitrarily excluding some studies from consideration.

Reports for several groups which have discussed and published statements on criteria for experimental design and data interpretation were entered into evidence, as were the API alternative approach and the Hooker Chemical Company alternative approach. As seen below, these documents all support the contention of OSHA witnesses that no simple formula for bioassay design or interpretation can be made, and that the most useful aproach is to set out general criteria and considerations for expert review. These reports on criteria which were entered into evidence were as follows:

a. International Agency for Research on Cancer. 1978. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man;

b. Food Safety Council. 1978. Proposed System for Food Safety Assessment;

c. Environmental Protection Agency. 1978. Proposed guidelines for registering pesticides in the U.S., Hazard evaluation: Humans and domestic animals;

d. World Health Organization. 1974. Assessment of the Carcinogenicity and Mutagenicity of Chemicals;

e. National Cancer Institute. 1976. Guidelines for Carcinogen Bioassay in Small Rodents;

f. Health and Welfare, Canada. 1973. The Testing of Chemicals for Carcinogenicity, Mutagenicity and Teratogenicity;

g. International Union Against Cancer. 1969. Carcinogenicity Testing;

h. Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation. 1971. Panel on carcinogenesis report on cancer testing in the safety evaluation of food additives and pesticides;

i. Mrak Commission. 1969. Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health.

All these groups were in substantial agreement that certain factors need to be taken into consideration in the design and interpretation of carcinogenicity bioassay studies. These groups were largely concerned with negative studies. Despite this concern with safety studies, however, in almost no case was any specific recommendation made on exactly how the general considerations should be embodied in particular experimental designs or interpretation. Several reports specifically avoided prescriptions for protocols:

"The criteria which are described are general guidelines and not rigid, universal criteria. The complexity of the problem dictates that the evaluation of the potential human hazards of a given agent must be individualized in terms of the chemical and metabolic aspects of that agent . . ." (NCAB Report, 1977, p. 461; Exhibit B to Weinstein Statement)

(e) How should OSHA determine whether positive bioassay reports meet scientific criteria for acceptability?

OSHA clearly cannot prescribe a formula for judging whether a given bioassay is adequate to form part or all of the basis for regulation of human exposure. Such determinations will have to be made on a case-by-case basis by OSHA's experts. There was almost unanimous support for this approach voiced at the hearing. Dr. Paul Kotin (Johns Manville) made this point with unusual clarity when he said, "I know there is not a worker in the field who does not have a feel for what is an adequate study" (Kotin, Tr. 8648). Dr. Richard Griesemer (NIH) testified: "I think there is a consensus of opinion about what is a proper experiment after the experiment is over" (Griesemer, Tr. 932–933). Dr. Harold Stewart (NCI) made the following comment on experimental designs: ". . . [if] there are standards for setting up tests for evaluation a possible carcinogen . . . it would be a test that you could read through and say, 'good test' " (Stewart, Tr. 590). Dr. Ralph Yodaiken (NIOSH) was asked, ". . . how should the acceptability of the protocol be determined?" He replied, "There is no set of rules which an investigator has to follow. Each experimenter determines his own guidelines . . . then the protocol is acceptable . . . I do not think there is any set of fixed guidelines we have to follow or scientist [who] would be prepared to follow" (Yodaiken, Tr. 2891). Dr. Richard Bates (FDA) said: ". . . a variety of disciplines are needed, and people with expertise and experience are needed to make many phases of the evaluation . . ." (Bates, Tr. 592).

Support for a case-by-case approach to data evaluation also came from Dr. Golberg (CIIT), who said:

"Even more than in the past it is essential to treat each compound as a unique entity, and to consider all the relevant facts about it. Good science demands no less." (Golberg. Tr. 6486–6487)

Dr. Adrian Gross (FDA) summed up his feeling on this issue as follows:

"I feel that all we have to do is publish how we will assess the results . . . give the people the freedom to do whatever is right for them and for their own circumstances, as long as we state the rules of the game in advance . . ." (Gross, Tr. 1944)

c. OSHA's Conclusions

The issue of how OSHA will evaluate data from the animal carcinogenicity bioassays of diverse formats and quality was discussed in the proposed regulation and in this proceeding. The related question of whether OSHA should prescribe specific standards for the conduct of bioassays and for the evaluation of bioassay results was also addressed at the hearing.

The proposed regulation noted that the quality of bioassay data is indeed variable and such data need and will get careful scientific evaluation. The proposal further noted that broad scientific agreement exists on principles for evaluating bioassay data for purposes of regulation of human exposure to potential carcinogens.

OSHA concludes that it should not specify minimal or desirable standards of acceptability for studies yielding evidence of carcinogenicity. The great majority of witnesses testified in favor of OSHA's intention to rely upon informed scientific judgment for a flexible approach to evaluation of the adequacy and significance of bioassay data. Witnesses who alleged that there is a need for OSHA to specify protocols for conducting bioassays for judging quality and significance of bioassay data failed to provide evidence that specification of such protocols is desirable or feasible. Several witnesses testified that it would indeed be unnecessary, undesirable, and scientifically indefensible for OSHA to prescribe standards for use of bioassay data for regulatory purposes.

Previous consideration of these issues by various scientific experts and committees was reviewed at the hearing. Several groups have listed criteria for judging adequacy of negative bioassay data, but the criteria have typically been discussed only in general ways and prespecification of standards for such criteria has been largely avoided for all but the most basic experimental factors.

Specification of criteria for the acceptability of positive results was advised against by witnesses and has been avoided by most previous scientific groups. Most witnesses testified that evidence of carcinogenicity from bioassays should be evaluated by scientific experts to judge adequacy of the positive results.

Case-by-case expert scientific review appears to be the only feasible manner of evaluating positive carcinogenicity evidence. Thus, OSHA will judge adequacy of bioassay data by expert scientific review, and not by prescribing experimental or interpretative protocols in advance. It should be noted that this scientific review and exercise of scientific judgment is not intended to create any legal rights beyond those inherent in section 6(b) of the Act.

In summary, the field of carcinogenicity testing by means of animal bioassays is complex. There is simply no way to standardize experimental bioassays, nor is there a way to standardize means of interpreting results from bioassays. Dr. Arthur Upton (Director, NCI) explained this situation as follows:

"Many experiments raise specific problems of interpretation; the resolution of these problems requires evaluation by experienced professionals in several disciplines, and cannot be reduced to a formula." (Upton, S. 12)

Mr. Edward Baier (Deputy Director, NIOSH) explained the NIOSH position on experimental protocols and interpretation as follows:

Q: The NIOSH does not have criteria for the evaluation of animal studies?

A: Not a written policy as such.

Q: Does it have an unwritten policy?

A: Yes. I think as we discussed this morning, we could probably enumerate what a lot of the criteria are, unwritten.

Q: They exist, then, in the heads of the people that work at NIOSH?

A: Yes, as professional judgment. (Baier, Tr. 2989)

12. Should Tumor "Promoters" be Distinguished from Tumor "Initiators" and Regulated Differently?

a. OSHA's Proposal

In the preamble to the proposed regulation, OSHA made no distinction, for regulatory purposes, between those toxic substances that may "initiate" carcinogenesis and those toxic substances that might "promote" it.

b. The Public's Response and OSHA's Evaluation

A number of participants drew attention to the multi-stage nature of cancer and to supposed distinctions between the mechanisms of action of agents that are responsible for the first stage in cancer development ("initiators") and agents responsible for subsequent stages ("promoters"). One concise account of the difference between these classes of agents was presented by Dr. Bernard Weinstein (Columbia Univ.):

"We know that in both experimental animals, and in humans, carcinogenesis frequently results from the exposure not to a single substance but to several substances and that the evolution from a normal cell to a tumor cell is a multi-step process with different agents acting at different stages. It is possible to define at least two different types of agents as well as two distinct steps. The first types of agents are called initiating agent carcinogens, and are sometimes referred to as "solitary carcinogens." These compounds, when given at sufficient doses, produce tumors on their own. They also are frequently mutagenic when tested in mutagenesis assays.

"The second class of agents, called tumor promoters, by themselves do not produce cancer but enhance the activity of the initiating agents. If a very low dose of an initiating agent carcinogen is given to experimental animals, and this is followed by treatment with a promoting agent, the combination will produce a high incidence of tumors. The classical case of this phenomenon involves exposing the skin of mice to low doses of known carcinogens such as benzo(a)pyrene or N-Methyl N-nitrosourea. Although higher doses of these compounds by themselves will produce a very high incidence of tumors, the doses chosen are so low that by themselves, they produce no tumors or a very low incidence of tumors. At varying intervals a second agent, generally from a different class of compounds, is applied to determine if the combination of exposures will produce a significant incidence of tumors. If such a result occurs, we refer to it as syncarcinogenesis, and if the second agent would not by itself produce tumors even at high doses, that agent is classified as a promoting agent. In recent years this phenomenon has been studied in a variety of tissues, including colon and bladder.

"There is reason to believe that this interaction between these two different types of compounds could be important in the production of tumors in humans. For instance, asbestos workers who do not smoke cigarettes do not appear to have a higher incidence of lung cancer than other non-smoking individuals who do not work with asbestos. However, asbestos workers who smoke cigarettes have at least a ten-fold higher incidence of lung cancer than cigarette smokers who do not work with asbestos. So we have one agent, cigarette smoke, which at higher doses will by itself produce lung cancer. A second agent, asbestos, by itself will apparently not produce lung cancer.[2] However, when the two agents are placed together, there is a synergistic action.

"It is likely that the incidence of a variety of human cancers is not determined exclusively by exposure to initiating agents. It is possible that all of us are frequently

exposed to initiating agents, but that the rate-limiting step is the exposure to promoters. Thus, it is extremely important to identify promoting agents in the human environment." (Weinstein, S. 6–7)

Another account was presented in the report of the National Academy of Sciences' Committee for a Study of Saccharin and Food Safety Policy:

"In skin, liver, mammary glands, colon, and, probably, in most other tissues or organs in laboratory animals, carcinogenesis can be induced by a brief exposure to one type of chemical, an *initiating carcinogen,* followed by a prolonged exposure to other chemicals, called *promoting agents* or *promoters.* Promoters are often not able to initiate carcinogenesis by themselves or they do so very inefficiently. At best, they are carcinogens of low potency. Most carcinogens are capable of both initiating and promoting and, thus, can produce cancer by themselves after repeated or prolonged exposure.

"The apparent latent period between initiation and the appearance of cancer is not a true latent period. Rather, it is characterized by the presence of new cells that represent steps or stages in the slow cellular evolution from normal, through initiated, preneoplastic, and premalignant cells, to the ultimate malignant cells that characterized cancer. Generally, the new cells in the early phases grow quite slowly. They may have distinctive structural and biochemical markers that facilitate their identification with reasonable certainty. In humans, these lesions have been studied most thoroughly in the cervix and in the skin but now are receiving greater attention in the urinary bladder, breast, and respiratory tract, among other sites.

"The process of promotion appears to be essential for cancer development. For example, in tissues such as the skin and liver, changes in cells or tissues that have been induced by a brief exposure to a carcinogen may persist for most of the lifetime of an animal without undergoing further steps in the carcinogenic process. The essentially irreversible nature of the initiating events emphasizes the potential hazard for cancer development from even a brief exposure to a potent carcinogen.

"In contrast to initiation, many of the events that occur during the process of promotion and prior to the appearance of cancer appear to be reversible. The focal collections of altered cells that proliferate during the several steps and that fall under the general phenomenon of promotion may disappear with discontinuance of the promoting stimuli. Thus, for many chemicals, a continual exposure to a promoting environment over a relatively long period seems to be required for the development of cancer.

"The essential nature of the process of promotion is not understood. There is general agreement that a stimulus for cell proliferation is one component. However, this by itself is insufficient. Although the analysis of promotion is largely undeveloped, it appears that each organ or tissue may require its own special type of environment in order to select and encourage the growth and further evolution of those few cells that are altered during initiation. For example, croton oil and one group of its active derivatives, the phorbol esters, are potent promoters for the skin, phenobarbital for the liver, bile acids and cylopropenoid fatty acids for the colon, and prolactin and other hormones for the mammary gland. If this organ-specificity proves to be a general phenomenon in promotion, it poses major problems in the development of suitable general assay procedures for promoters and of appropriate guidelines for wise government regulation." (NAS, 1978, pp. 3–1–3–3).

A more detailed account presented by the National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis characterized initiating and promoting agents more precisely, and pointed out that they are often difficult to distinguish by means of the biological test systems presently available:

"Our understanding of the latency phenomenon in the natural history of carcinogenesis was pioneered by Mottram (1944), markedly accelerated by the studies of Berenblum and Shubik (1947, 1949), and further enhanced by Boutwell (1974), Van Duuren (1976), Hecker (1971), and others. The basic demonstration by Berenblum and Shubik was that skin carcinogenesis could be divided into a state of *initiation,* which resulted from the direct administration of a known chemical carcinogen such as a polcyclic hydrocarbon, followed by a second stage of promotion, which necessitated the repeated application of another agent, termed the promoting agent. The promoting agent alone was essentially incapable of inducing the neoplastic transformation. Several characteristics of initiating and promoting agents are now recognized. These qualitative differences in the two stages are summarized in Table 5.

"Promoting agents exert effects which can be modulated by the environment. Boutwell *et al.* (1949), Tannenbaum (1944), and others (Slaga *et al.,* 1978) demonstrated the effect of nutrition on tumor promotion, with respect to both the quality and the quantity of nutritional components given to animals undergoing carcinogenesis. Furthermore, Boutwell (1964) demonstrated by subtle dosage regimens that promotion could be reversed under appropriate circumstances. Retinoids, for example, can inhibit the biochemical effects of promoting agents in the skin (Verma and Boutwell, 1974) and the appearance of several types of neoplasms (Sporn, 1978). Finally, promoting agents for the skin, especially the phorbol esters, cause the development of a few neoplasms on prolonged administration. Although some investigators have attributed this finding to a weak carcinogenicity of the promoting agents, an equally plausible explanation is that efficient promoting agents, on repeated administration, may promote cells initiated by radiation or chemicals in the environment such as or by spontaneous errors. Although the latter concept makes a clear distinction between the initiating and promoting agents, it also raises difficulties in distinguishing clearly between weak carcinogens and promoting agents by the biological test systems presently available.

"One may characterize initiating and promoting agents in terms of their biological and their molecular function, with the understanding that such definitions are not yet definitive but encompass the facts as presently known. Since, under certain circumstances, initiators are mutagenic and promoters are not, the following definitions are appropriate:

'Initiating Agent—an agent—chemical, physical, or biological—capable of directly altering the native molecular structure or the genetic component (DNA) of the cell. Such alteration(s) may be the result of a covalent reaction of DNA with the initiating agent itself or with one of its metabolites. Such alteration may also include distortion of the structure of DNA without covalent alteration of its components. Finally the agent may cause one or more complete scissions of the DNA chain, an elimination of one of its component parts (e.g., bases or sugars) or errors in reading or repair by DNA polymerase. Such capabilities of an initiating agents do not in themselves prove that alteration of DNA is an absolute requirement for the neoplastic transformation.

'Promoting Agent—an agent, that alters the expression of genetic information of the cell. Examples of such agents include hormones, drugs, plant products, etc. which themselves do not directly react with the genetic material but rather affect its expression by a variety of mechanisms including cell surface receptors, cytoplasmic and nuclear protein receptors, or an alteration of other cellular components and functions.

'Traditionally the bioassay of tumor promoters has been done in whole animal experiments, but there have been recently described a few systems in cell culture, in which tumor promoting action can be observed (vid infra). Like some initiating agents and complete carcinogens, promoting agents show a significant degree of specificity with respect to the tissue in which they exert their effects, e.g., phenobarbital in the liver but not in the skin. Furthermore, the endocrine state, nutritional state and age of the animal are modifying factors in the response to both initiating and promoting agents (Slaga *et al.,* 1978).

'Given the characteristics of promoting agents, one of their important effects is to decrease significantly the time between the application of the initiating agents and the appearance of the final neoplasms. This effect, verified numerous times by experimental studies, can also be applied to the "spontaneous" appearance of neoplasms in animals. Peraino and his associates (1975) reported that phenobarbital induced a decrease in the latency time for spontaneous hepatoma production in the mouse. Thus, promoting agents administered to animals for extended periods without a knowledge of the lifetime spontaneous incidence of neoplasia may give results which label a promoting agent as an initiating agent." (NCAB, 1979, pp. 12–14)

Characteristics of Stages of Initiation and Promotion in Skin Carcinogenesis

(From NCAB, 1979, Table 5)

Initiation	Promotion
Irreversible with "memory"	Reversible, at least in early stages.
Initiated cells and immediate progeny not usually indentifiable	Promoted neoplasm seen grossly.
"Pure" initiation (incomplete carcinogen) causes irreversible change but no neoplasm unless promoter applied.	Promoting agents not carcinogenic but may promote cells fortuitously initiated cells (i.e. background).
Dependent on cell cycle and, for many chemicals, on the metabolism of the cell.	Modulated by diet, hormonal, environmental, and related factors.

A number of witnesses suggested that OSHA should take account of the distinctions between initiating and promoting agents in its rules for identification, classification and regulation of substances posing potential carcinogenic risks. For example, Dr. Emmanuel Farber (Univ. of Toronto) made the following statement:

"As our knowledge of the sequences of events involved in carcinogenesis increases, we can no longer regard chemical carcinogenesis as a simple one-stage or two-stage process. Rather, cancer seems to develop progressively through a number of stages, each of which can be influenced by chemicals or other environmental factors, interacting with host factors such as nutrition, hormone levels, etc. Any proposal for identification and classificaton of carcinogens should recognize this complexity." (Farber, S. 4, citing Farber, 1978; Appendix D to Farber Statement)

Dr. Paul Kotin (Johns-Manville) quoted the following statement:

"Carcinogenesis appears to consist of at least two separable stages, initiation and promotion. Initiation is an irreversible process that can be produced by *sufficient treatment* with a *subcarcinogenic dose* of a physical or chemical carcinogen, while promotion is a reversible process requiring repeated application of a promoting agent that ultimately stimulates the initiated cells to give rise to a tumor. . . . Since most, if not all, chemical carcinogens interact with DNA . . . it seems reasonable to assume that alterations in DNA (somatic mutations) may give rise to an initiated cell. However, epigenetic mechanisms cannot be discounted. . . .The mechanisms responsible for promotion are unknown and, while stimulation of cell replication is required, this does not in itself appear to be sufficient . . . . The effect of promoters on gene expression and other cellular metabolic processes may be indispensible." (Kotin, S. 17–18, quoting Yager and Potter, 1975)

AIHC introduced an article by Jean L. Marx which suggested that the distinction between initiating agents and promoting agents may eventually justify different strategies for cancer prevention:

"The distinction between initiation and promotion has important implications for public health because the initiation step of the process eventually leading to tumor formation is irreversible. But promotion is reversible. If the exposure ceases before the cells gain the ability to multiply in the absence of the promoter, then tumor formation may be avoided.

"Moreover, investigators have shown that certain agents inhibit tumor promotion even in the presence of the promoting agent."

* * * * *

"But there is an even greater significance to the existence of promotion inhibitors. Several investigators have pointed out the improbability of ever removing all chemicals capable of initiation—which only requires one exposure and is irreversible—from the environment. But the effects of promotion are reversible if the promoter can be removed in time, and even if it cannot be removed, it may be possible to use inhibitors to prevent cancers from developing. Thomas Slaga of Oak Ridge National Laboratory, for example, has observed a synergistic inhibition of promotion by a combination of a steroid with a vitamin A derivative at doses at which neither of these agents is toxic. Thus, although many questions about the mechanism of tumor initiation and promotion remain unanswered, the investigators hope that the research will lead both to a better understanding of chemical carcinogenesis and ultimately of strategies for preventing it." (Marx, 1978, pp. 515 and 518; Hearing Exhibit 219)

Mr. Richard Peto (Oxford Univ.) suggested that some distinction might be made between mutagenic carcinogens, which he believed are likely to be initiators, and non-mutagenic carcinogens, which he believed are unlikely to be:

"Nearly all the compounds where difficulties, both either theoretical or real, arise are substances which are carcinogenic for animals but which are not mutagenic, and I would suggest that regulations be drawn up in such a way as to distinguish between these, perhaps by a difference in emphasis rather than a quantitative difference, but that some distinction be made. Perhaps that mutagenic carcinogens perhaps, you know, should be treated presumptively as proposed but that rebuttal should be invited. The exact phraseology is much better left to lawyers than to somebody who tries to be a scientist." (Peto, Tr. 2518)

Dr. Robert Squire (Johns Hopkins Univ.) made a somewhat similar suggestion (Squire, S. 19).

Apart from these suggestions by Mr. Peto and Dr. Squire, OSHA believes that the comments in the Record on this issue were generally of a non-specific nature. Although several witnesses suggested that promoters are in some way of less concern than initiators, none offered a specific, operationally explicit procedure for identifying or regulating promoters less stringently than initiators. As Dr. Richard Bates (NIEHS; FDA) pointed out, we do not have sufficient knowledge at the present time to identify promoters unequivocally as such or to establish "threshold" levels of exposure to them:

"Another class [of chemicals] would be promoting agents. In the experimental skin carcinogenesis model for which this terminology was developed, it is recognized that these agents have little or no carcinogenic effect themselves, that they markedly enhance the carcinogenicity of certain carcinogenic chemicals, and that their effect requires repeated exposure and is reversible in the absence of such repeated exposure. Since the mechanism by which this effect occurs in the skin has still not been adequately worked out, it is difficult to know how widespread this phenomenon is for various chemicals and organ sites. Thus, although this is probably a class of chemicals affecting the incidence of cancer that many would regard as likely to have a threshold, there are usually practical problems involved in knowing whether or not to place a chemical in this class from the amount of data generally available to the regulator. There are also problems involved in deciding at what level such a threshold may exist, and there is little information on how a multiplicity of such chemicals in the human environment may interact in a additive, synergistic, or inhibitory way." (Bates, S. 16–17) (footnote omitted).

Dr. William Lijinsky (NCI-FCRC) made a similar point:

"While this model [initiation-promotion] is interesting and philosophically satisfying, the evidence that it has relevance to types of cancer other than skin, in animals or in man, is very flimsy. There are inconsistencies even in the animal model itself, in that it only works in certain strains of mice, even for the skin, and not in rats or in hamsters. Likewise, it seems to work well only when polynuclear compounds are the initiators, since the potent alkylating agents nitrosomethylurea and nitrosomethylnitroguanidine, although skin carcinogens themselves, are very poor initiators and give rise to only very small increases in skin tumors when their application to mouse skin is followed by Croton oil treatment. This reveals, yet again, how little we know about the mechanism of carcinogenesis and how risky it is for us to base decisions which might jeopardize human health on such uncertain bases." (Lijinsky, S. 17)

There are a number of other serious practical difficulties. As NIOSH pointed out (S. 16), the terms "promoting agents" and "co-carcinogens" are "widely and variously used—without the same meanings to everyone." As the NCAB Subcommittee on Environmental

Carcinogenesis pointed out, existing biological test systems are not capable of identifying promoters clearly (NCAB 1979, pp. 12–14). Indeed, all known promoting agents also have at least weak tumorigenic activity (Van Duuren 1976, p. 29). It would be difficult for OSHA to adopt Dr. Squire's proposal to regulate non-mutagenic carcinogens less rigorously, because several chemicals well established as carcinogenic in humans are not mutagenic (e.g. asbestos, nickel, diethylstilbestrol). This issue was put in perspective in the recent report of the Office of Science and Technology Policy:

"It has been argued that a chemical which only increases an already high rate should be viewed as a promoter or co-carcinogen (rather than a direct-acting carcinogen) and treated differently in the regulatory process. While such an argument may have merit, current routine laboratory methods do not generally allow one to distinguish promoters or co-carcinogens from direct-acting carcinogens. Laboratory protocols for demonstrating promoter effects have not yet been adapted to test schemes. Until such methodology becomes available, we believe that a chemical which increases the cancer incidence rate in laboratory animals should be viewed as a potential human carcinogen and treated accordingly by regulatory agencies." (OSTP, 1979, p. 10).

The last conclusion has been endorsed by others in recent years:

"The two stage mechanism has not been convincingly demonstrated in carcinogenesis in sites other than the skin. There are many situations in which a two-stage mechanism appears as an attractive explanation. We are still at a stage where much more study is needed before many of these concepts, valid for the skin, can be said to have general application. From a practical standpoint it is apparent that croton oil or substances of similar activity would pose a considerable hazard to the skin. Although such interactions may pose an important public health problem, our present state of knowledge does not make it practical to recommend routine tests for cocarcinogenicity or promoting action; if circumstances suggest the existence of such action, testing should take this into account. This area needs intensive study." (FDA, 1971, p. 423)

* * * * *

"In this document the term "carcinogen" is used in its broad sense, because in most of the current human epidemiologic approaches and certain animal bioassays it is not possible to differentiate clearly between initiating agents, promoting agents, and certain modifying factors. Any factors or combination of factors which increases the risk of cancer in humans is of concern regardless of its mechanism of action." (NCAB Report, 1977, p. 461)

This position was endorsed by several expert witnesses, including Dr. Arthur Upton (Director, NCI). Dr. Bernard Weinstein (Columbia Univ.) and Dr. Benjamin Van Duuren (New York Univ.):

"Because of incomplete knowledge concerning mechanisms, I also do not believe that distinctions between "carcinogens" and "co-carcinogens", or between "causative agents" and "enhancing agents" can be considered relevant today when ascertaining hazards to human health arising from carcinogens. In safety testing of carcinogens today, we are concerned with one question: "Does exposure to the test agent result in a significant induction of tumors in exposed populations as compared to controls?" If so, then the test agent has elicited a carcinogenic response and must, therefore, be considered potentially hazardous to human health. Precise knowledge of the mechanism of action of the carcinogen or of possible co-factors in the host animal is not required for preventive action unless and until we have such knowledge, it is difficult to make practical distinctions between "carcinogens" and "co-carcinogens" and between "causative agents" versus "enhancing agents".(Upton, S. 16–17)

* * * * *

"I agree with the OSHA proposal that no distinction should be made between the induction of tumors and the enhancement of tumor incidence in rodent bioassays." (Weinstein, S. 3)

* * * * *

". . . a number of air pollutants, phenols, and long chain aliphatic hydrocarbons are known to have co-carcinogenic or tumor promoting properties (18). In addition, cigarette smoke, a complex mixture or organic compounds, contains both initiators and promoters. In light of the continuous exposure to these substances, there is no theoretical reason to believe that exposure to even a very small additional amount of another carcinogen, cocarcinogen, or tumor promoter would not lead to tumor induction." (Van Duuren, S. 8)

c. OSHA's Conclusions

For these reasons, OSHA concludes that it would not be practicable or justifiable to establish different criteria for the identification, classification, or regulation of initiating and promoting agents. OSHA agrees with the NCAB Subcommittee that "any factor or combination of factors which increases the risk of cancer in humans is of concern regardless of its mechanism of action." This is particularly important in the occupational setting, in which the likelihood of periodic exposure to initiators makes the occurrence of promoters of special concern.

13. Should Metabolic and Pharmacokinetic Information be used in the Identification or Regulation of Potential Carcinogens?

a. OSHA's Proposal

During the course of the public comment period, the question was raised repeatedly whether OSHA should take into account data on pharmacokinetics and metabolism in identifying, classifying and regulating potential carcinogens. While some participants claimed that OSHA had rejected such an approach, the preamble to the proposed regulation clearly stated:

"OSHA is not aware of any single molecular configuration, structural characteristic, or physical property of chemical carcinogens that can be pinpointed as the crucial cancer inducing element or site. One explanation may be that a substance may be metabolized to a different form when exposed to the test model or man and that metabolite [may] be the carcinogen, rather than the substance itself. However, gross similarities in chemical reactivity and metabolic fate in the host can be identified for many chemical carcinogens. This followed the discovery by the Millers that metabolic conversion of environmental chemical carcinogens can occur in the host with the ultimate formation of the "proximate" or "active" form of the chemical carcinogen." (42 FR 54168)

OSHA did, in other words, recognize that interspecies differences in metabolism and pharmacokinetics may exist and can complicate the prediction of carcinogenic activity. In discussing the problems of using structure-activity correlations for predicting carcinogenic effects of untested compounds, OSHA also commented:

". . . there are the compounding factors of dose dependent variations in metabolic fate, species differences in anatomic and metabolic fate, and the influence of related compounds (summation, synergism or inhibition) upon chemical carcinogens when present simultaneously either in the environment or in the host." (42 FR 54168)

At the time of the proposed regulation, OSHA was following the lead of expert committees which did not explicitly list metabolism and pharmacokinetics as factors to be considered in evaluating the carcinogenic potential of a compound. In a report of the panel on Carcinogenicity of the Cancer Research Commission of the UICC, the panel commented on the role of metabolic studies in routine carcinogenicity testing:

"In the opinion of the Panel, studies on metabolic changes of carcinogens in the body should not, in general, be part of a bioassay programme designed to detect carcinogens in man's total environment. Too little is known at present about the metabolism of established carcinogens to enable the design of useful experiments for routine testing centres." (UICC, 1969, p. 35)

The Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens commented that metabolic characteristics or abnormalities may

modify the development of neoplasia but concluded:

"Understanding of their specific effects in man, however is still not adequate to serve as a reliable basis for preventive action." (NCI Ad Hoc Committee, 1970, p. 4; Exhibit 10b to Epstein Statement)

A NAS report on *Contemporary Pest Control Practices and Prospects* had commented:

"Research on molecular mechanisms in carcinogenesis has provided evidence that the actual carcinogen is often not the compound administered but instead is a metabolite of that compound (Miller and Miller 1971). Active carcinogens tend to possess particular features of chemical structure by which they may be recognized. Although apparent exceptions are known, similarities in the metabolic fate of a compound in different species may imply similar carcinogenic properties. Hence, metabolic studies using human and animal tissues can support the case that a given compound that is carcinogenic in animals may or may not be carcinogenic in man. At present, however, such information is available only for very few compounds." (NAS, 1975a, pp. 66, 74; Appendix H to Rall Statement)

A Report of the World Health Organization (WHO) discussed the role of metabolic activation in modifying the carcinogenic potential of chemicals and commented that:

"Although the facts of interaction of the active form of chemical carcinogens with cellular macromolecules are well established, the significance of these interactions for carcinogenesis is not yet understood." (WHO Tech. Report No. 546, 1974, p. 7)

Finally, the FDA in publishing *Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Food Producing Animals* summarized the comments they had received regarding the use of metabolic data:

"Numerous comments were received on the proposal's requirement for metabolic studies. Several comments stated that there should be no attention paid to metabolites. Others contended that metabolism studies should not be routinely required on the ground that the pathway of excretion is of no toxicological importance if all of the administered compound has been eliminated from the tissues of the target animal. Most comments recommended that a metabolism study should only be required to determine the major metabolites in the edible tissue of target animals, suggesting that the public health would not be served if petitioners are required to pursue endless structural elucidations and quantitations of all metabolites even though some of them might constitute minor fractions of the residue of the sponsored compound. Comments also contended that it may not be experimentally possible to administer to animals sufficient quantitities of a compound to obtain amounts of residues sufficient for structural identification. Several comments asserted the studies should be limited to identification of residues in the edible tissues of target animals and that generally it would be unnecessary to have such information on metabolites in inedible tissues. Further, some comments stated that radiotracer studies can be employed to determine the time by which the sponsored compound and its metabolic products are eliminated ("out time"). However, other comments suggested that all metabolites should be identified and tested for toxicity. (42 FR 10416)

FDA's analysis of these comments appears to reflect the fact that some interests generally oppose the use of metabolic information as part of a safety testing scheme, in sharp contrast to the position of the same interests in this proceeding, who urged that metabolic information be required as part of a system for identifying carcinogens.

b. The Public's Response and OSHA's Evaluation

OSHA is aware that, subsequent to the publication of the proposed regulation in this rulemaking and the subsequent hearing, several committees and agencies have recommended or proposed that metabolic and pharmacokinetic information should be used in the evaluation of carcinogenic risk. The EPA's *Proposed Guidelines for Registering Pesticides* include a section on metabolic data:

"Metabolism studies are designed to provide information on how a pesticide moves, changes, or accumulates in the mammalian system. The field of metabolic studies can be quite broad and a number of very complex tests would be needed to define precisely how a single compound is processed in the mammalian body. Data from a general metabolism study would be required to support the registration of all pesticide products for which chronic data are also required. The study, as proposed here, is designed to identify the significant metabolites produced from a pesticide and to determine how long and how much a pesticide and its metabolites are stored in various tissues of the body.

"Data from a general metabolism study would be used primarily to indicate the need for additional or special toxicity testing. For example, EPA could compare the major animal metabolites (metabolism data), with the compounds which are formed by degradation of a pesticide in the environment (environmental chemistry data). This comparison would show whether an environmental breakdown product is also produced by animal metabolism. If not, humans might be exposed to a compound on which the Agency had no toxicity data, since the breakdown product is neither part of the substance normally tested under the guidelines nor is it formed by metabolism of the test substance. The general metabolism studies might also indicate that levels of a pesticide or a metabolite in body tissues increase steadily with repeated dosing. The Agency is particularly concerned with such bioaccumulative compounds. Tissue concentration of a bioaccumulative pesticide could eventually build up to a toxic level as a result of long-term, low-level exposure. With such information, EPA would give particular attention to the evaluation of chronic toxicity test data." (43 FR 37349)

The Food Safety Council's report included a chapter on "Metabolism and Pharmacokinetics" and made the following recommendation:

"Increased understanding of the value and applicability of pharmacokinetics has led to the recognition that metabolic and pharmacokinetic data are not merely ancillary information but constitute vital mainstream characteristics of the compound, to be used in planning both the strategy and tactics of the approaches to safety evaluation. Metabolic and pharmacokinetic information is central to the design of protocols, leading to proper species selection, definition of dose regimens and the appropriate conduct of both in vivo and in vitro tests. Intelligent application of metabolic and pharmacokinetic information is one of the principal weapons that permits the selection of appropriate tests and conditions specifically tailored to the characteristics of the individual compound under study. Thus, in the plan of investigation developed herein, metabolic comparability between man and the animal species proposed for use in a long-term test will be established before any such test is initiated." (Food Safety Council, 1978, p. 65; Hearing Exhibit 227)

It should be noted that both these reports recommended the use of metabolic and pharamacokinetic data as part of the design of a series of tests to establish safety. Neither was concerned with the retrospective evaluation of tests showing positive results, the problem generally facing OSHA.

The Safe Drinking Water Committee of the NAS suggested that metabolism studies are useful for *quantitative* assessments of carcinogenic risk:

"Despite wide gaps in our knowledge of the metabolism and ultimate fate of chemicals in man, properly conducted experiments will yield results that can improve our estimates of the risk to human populations from long-term exposures." (NAS, 1977, p. 27; Appendix I to Rall Statement)

Some participants criticized OSHA for not listing metabolism and pharmacokinetics as factors to be taken into account in the *qualitative* identification of carcinogens. The AIHC Recommended Alternatives stated:

"OSHA's proposal sanctions extrapolation from mammalian test data to human exposure but ignores major metabolic, pharmacokinetic and biochemical differences which exist between species of animals and man." (AIHC Recommended Alternatives, p. 36)

The American Iron and Steel Institute (AISI, Post-hearing Brief, p. 13), also criticized OSHA for not listing these factors in the proposed regulation.

Other witnesses simply urged that OSHA should consider such data in the final regulation: Dr. Raymond Yang (Carnegie-Mellon), S. 4; Dr. Mitchell Zavon (NACA), Tr. 5406; Dr. Carroll Kirwin (Phillips Petroleum), Tr. 4208; Dr. Harry Skalsky (Reynolds Aluminum), Tr. 7597; Dr. Ralph Freudenthal (Stauffer Chem.), Tr. 6748–6757; Dr. Marvin Friedman (Allied Chemical), S. 6–8; and Dr. Miro Todorovich (National Center for the Public Interest), Tr. 7967.

The comments and testimony received on this issue can be divided into three principal areas of question:

1. In what circumstances would metabolic and pharmacokinetic information be sufficient to rebut the qualitative presumption that a chemical found to be carcinogenic in animals presents a risk to humans?
2. Is our knowledge of metabolism and pharmacokinetics sufficient for this information to be useful in practice in a significant number of cases?
3. Can specific procedures or criteria for the use of metabolic and pharmacokinetic information be laid down on the basis of our present knowledge?

1. *In what circumstances would metabolic and pharmacokinetic information serve to rebut a qualitative presumption of risk?*

The only extensive body of evidence relevant to this question is that related to the hypothesis of "metabolic overloading". This evidence was presented to show that metabolic and pharmacokinetic information should be used in selecting high dose levels to be used in chronic toxicity testing, and that if it were not so used, positive results obtained at high doses might not be valid as a basis for qualitative extrapolation of risks at low doses. This evidence has already been reviewed in detail (See section 3. *Testing at High Doses).* The only other way in which metabolic and pharmacokinetic information would appear to invalidate the extrapolation of positive results in animals would be to show that a chemical is metabolized in humans in a qualitatively different way from that observed in animals. Specifically, OSHA believes that before any such information so used, public health considerations would dictate that it should be reasonably shown that the active carcinogenic metabolite in animals is *not* produced in human tissues. Although a number of witnesses implied that such evidence should be sought, no witness offered a specific example of such a qualitative difference having been observed. However, the evidence that such a circumstance might occur will be reviewed critically in the next section.

2. Is our present knowledge of metabolism and pharmacokinetics sufficient to be useful in practice?

(a) *Limitations of data.* Our present ability to use metabolic and pharmacokinetic information is greatly limited by the paucity of specific data available. For example, several witnesses were asked if they knew of any substance for which the metabolite which is known to be the ultimate carcinogen in animals, is *not* produced in human tissues. No one knew of such a chemical or study (See Goldman, Tr. 4480; Yang, Tr. 6824–5; Harris, Tr. 2075; Hoel, Tr. 2194). Indeed, the number of chemicals for which the ultimate carcinogenic metabolite in animals is known is quite small (See Goldman, Tr. 4480; Yang, Tr. 6824–6825; Gehring, Tr. 5175). The difficulty then lies in establishing if humans metabolize the chemical through the same pathway to the same ultimate carcinogenic metabolite as that found in animals.

Other witnesses pointed out that it would be unethical to conduct the experiments in humans which would be necessary to demonstrate that humans do not metabolize a compound to the identical ultimate carcinogen found in animals:

"We need to know the mechanism of carcinogenesis in the animal, and then we could perhaps find out if the mechanism were the same in man, which would be a sort of an experiment that properly would not be condoned, having identified a carcinogen in animals. I doubt if anybody would want to be exposed to such a compound at a dose that might induce cancer." (Lijinsky, Tr. 1055)

Another witness who also expressed this concern was Dr. Benjamin Trump, (Univ. of Md.) Tr. 2016.

Dr. Peter Goldman (Harvard Univ.) best summed up the uncertainties of defining the ultimate carcinogen for humans while discussing how many tissues would have to be examined before one could conclude that the human did not activate the compound:

". . . the more tissues one examined under the more ideal experimental conditions and found that nothing happened, the more certain our conclusion would be that human tissues do not activate this. But again, somebody may find a system where he can get those tissues to perform, but that becomes increasingly less likely as more data is piled up on the negative side. So I think one can never conclude with certainty that human tissues do not activate." (Goldman, Tr. 4478–4479)

Dr. Ronald Hart (Ohio State Univ.) expressed his concern over the lack of comparative metabolic data necessary to make such determinations:

"In other words, to see if there is any comparison between metabolic activation, and detoxification also has to be taken into consideration here, too. How long are these things around?

"And again, there just is not the data available, Ian. In other words, this pretty well summarizes the comparative approach, comparative evolutionary approach. It is a paucity of data; it is absolutely terrible." (Hart, Tr. 3500)

Dr. David Hoel (NIEHS) also commented on our lack of knowledge:

"I mean, what you have said theoretically is plausible in terms of having . . . the metabolite that is identified as being carcinogenic in the rodent not existing in man. I mean, that is, you know, conceivable. I cannot cite you any cases where that indeed is the situation, but, you know, theoretically it is a possibility.

"What I would worry from the practical standpoint is have we identified all the metabolite[s], do we really know what metabolite is the carcinogenic one, or have them all identified in the rodents, and are we sure that we have the metabolites identified in the human and none of those, although they may include some or not some of the ones in the rodents, whether or not we have those identified and the carcinogenic ones do not exist in man.

"Now, you know, practically I do not know if, you know, in today's time whether we are in a position to come up with such information." (Hoel, Tr. 2194)

The limitations of our knowledge were also expressed in a number of expert committee reports. The Safe Drinking Water Committee in their report *Drinking Water and Health* pointed out the usefulness of metabolic and phrmacokinetic data but commented that "there are few, if any, substances for which such understanding is at hand" (NAS, 1977a, p. 23). They stressed the difficulties in using these data to assess long term effects in humans, resulting from wide variations in metabolic and pharmacokinetic processes within the human population:

"In the last decade, large genetic differences in metabolism of toxic agents have been found in man, and study of these effects has led to a new branch of pharmacology—pharmacokinetics. The range of variability is illustrated by the observation that, in a group of about 20 patients, the steady-state plasma concentrations of two tricyclic antidepressants varied by about 30-fold, and the half-time of disappearance from the plasma varied about 10-fold (Hammer and Sjoqvist, 1967). Also, the plasma concentration of isonicotinic acid hydrazide has been found to vary by a factor of almost 100 in different people, and this appears to be genetically controlled (Weber, 1976).

* * * * *

"Many sources of variation within the population of any species, such as age, sex,

pregnancy, disease, can affect the response to foreign substances. An example is the difference between sexes in metabolism and toxicity of acetylsalicylic acid (Menguy et al., 1972).

"In addition, such environmental variables as temperature, lighting, barometric pressure, humidity, and diet are known to affect the toxicity of environmental pollutants. For example, the oral absorption of pentobarbital is greatly altered by the prior ingestion of a small cheese sandwich. In this case, peak pentobarbital concentration in plasma is diminished by about 50%, and the duration of the effective plasma concentration is doubled (Bush et al., 1966).

"Another difficulty in extrapolating from laboratory animals to man is the dose-duration problem. The lifetime of a mouse is about 2 yr. A man's life expectancy is close to 70 yr, and a woman's 5 yr longer. Because man usually excretes compounds more slowly than mice, this means that man, with a very small daily intake, can develop a greater accumulation of a compound over many years. (NAS, 1977a, pp. 35, 36; Appendix I to Rall Statement)

The Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens commented that metabolic characteristics or abnormalities may modify the development of neoplasia but concluded that:

"Understanding of their specific effects in man, however, is still not adequate to serve as a reliable basis for preventive action." (NCI Ad Hoc Committee, 1970, p. 4; Exhibit 10b to Epstein Statement)

A recent paper by Weiner and Newberne pointed out several specific limitations inherent in using metabolic and pharmacokinetic data to estimate carcinogenic risk for humans:

". . . comparisons of drug blood concentrations, and even tissue concentrations in various species, have often been disappointing in terms of the expected predictability of the safety of the drug in man from such studies.

"It is a small wonder that there has been a great deal of interest in studying the metabolites of drugs to help predict safety in man from animal studies. A few years ago it became fashionable to seek predictability by selecting test species which resembled man in terms of drug and metabolite blood and urine concentrations. The need for human biochemical data with doses of therapeutic magnitude at times limited the applicability of this principle. More limiting, however, is a wide spectrum of factors (Plaa, 1976) as a result of which predictability of human safety is not necessarily better in species which appear to have blood and/or urinary metabolite patterns judged to be "similar" to man. Important differences in predominant metabolic pathways are often not reflected in the concentration patterns (Gillette, 1977). In fact, even differences in tissue binding when metabolic pathways are similar can lead to the seemingly paradoxical situation of greater toxicity in the species with a shorter half-life in the blood (Zak and Weiner, 1975). It is not just the presence of metabolites, but their nature and distribution in each species that help determine the reaction they will cause." (Weiner and Newberne, 1978, pp. 231–232)

Weiner and Newberne also pointed out that:

". . . some of the toxicologically most troublesome metabolites are those which are formed in small, even minute, amounts and may be highly reactive, a fact which may contribute to both their toxic action and likelihood of escaping biochemical detection." (Ibid., 1978, p. 232, citing Gillette, 1977)

The authors concluded:

"Our ability to better predict human safety from animal toxicological studies will not come from irrationally expanding the variety and magnitude of "routine" tests but by selectively augmenting an appropriate spectrum of empirical toxicological studies consistent with the nature of each specific problem." (Ibid. 1978, p. 233, citing Gillette, 1977)

Dr. Umberto Saffiotti (NCI) also pointed out limitations in our knowledge of metabolism and mechanisms of action in his written testimony:

"I wish to stress that the study of the mechanism of action of carcinogens in human tissues is still in an early stage of development and I do not expect that it could be used in the near future to determine in a definitive manner that a given substance, known to be carcinogenic in animals, is entirely without any carcinogenic risk in humans. I do believe, however, that this methodology will bring about a much more accurate understanding of the differences between human and experimental animals in the metabolic requirements for activation of carcinogens and in the susceptibility to their effects. The major observations so far made show the qualitative similarity of the interactions of carcinogens with target tissues from experimental animals and humans, and the high quantitative variability of the human response among different individuals. Work along these lines will make it possible in the future to recognize particular susceptibility factors or markers which may allow us to identify the individuals in a population who are at a particularly high risk from exposure to a given substance or group of substances. A prudent policy of cancer prevention requires protection of the most sensitive individuals in the population." (Saffiotti, S. 42–43)

(b) *Available techniques and knowledge.* Dr. Raymond Yang (Carnegie-Mellon) presented in detail a specific technique to identify and measure metabolic differences between animals and humans. He described this method, "Comparative Metabolic Profile Analysis" as follows:

3.1.1 "The test chemical, labeled with radioisotope, is introduced by the route to be used in the chronic toxicity studies to an animal species most commonly used in chronic toxicity studies (i.e., rat, mouse, hamster, guinea pig). For the sake of convenience, the rat will be used as an example in the subsequent steps.

3.1.2 An *in vivo* metabolic profile is generated by chromatographic method using the first 24-hr urine sample from the rat.

3.1.3 The radioactive test chemical is incubated with rat tissues (liver, kidney, lung) under adequate tissue maintenance conditions. Generally, the liver, being the principal organ for the metabolism of foreign chemicals, is the only tissue needed for this step.

3.1.4 An *in vitro* rat metabolic profile is generated by the same chromatographic method using the incubation medium from the preceding step.

3.1.5 The radioactive test chemical is incubated, under similar conditions as above, with human tissues (liver, kidney, lung) obtained from local hospitals by surgical procedures or autopsies.

3.1.6 An *in vitro* human metabolic profile is generated similarly as above.

3.1.7 Compare the three metabolic profiles, i.e. rat *in vivo*, rat *in vitro* and human *in vitro*.

3.2 The rationale of this approach may be best demonstrated by the following equations: If Rat *in vivo* approximates Rat *in vitro* and Rat *in vitro* approximates Human *in vitro* then Rat *in vivo* approximates Human in *in vivo*.

3.3 In the event that the rat metabolic profiles do not match that of man, similar comparisons should be made on other species (mouse, hamster, guinea pig). The species and/or strain which most closely resembles man is the animal of choice." (Yang, S. 5–6)

Drs. Benjamin Trump (Univ. of Md.) and Curtis Harris (NCI) also presented data on experimentation they are conducting into the metabolic similarities between humans and animals. Specifically, this research involves using *in vitro* techniques for measuring inter- and intra-individual as well as interspecies variations in the metabolism of chemicals by human and animal tissues. Dr. Harris has focused on the identification of host susceptibility factors in humans. Several examples of chemicals tested in this system were described:

"Initial investigations are directed toward elucidating the metabolism by human tissues of chemical procarcinogens that are found in the environment. Since the binding of carcinogens to cellular macromolecules, i.e., the formation of adducts, is considered to be an important step in carcinogenesis (3), we have measured the capability of cultured human tissues to form such adducts. The chemical procarcinogens, 7, 12-dimethylbenz[a]anthracene, 3-methylcholanthrene, benzo[a,h]anthracene, dimethylnitrosamine, diethylnitrosamine, N-nitrosopiperidine, N-nitrosopyrrolidine, dinitrosopiperazine, and 1,2-dimethylhydrazine have been shown to be metabolically activated by human bronchus,

pancreatic duct and/or colon (4–11). The pathway of metabolic activation of benzo[a]pyrene in cultured human bronchus and the molecular structure of the major adduct between DNA and benzo[a]pyrene has been identified (7,8,12). It is important to note that this adduct has the same molecular structure as the benzo[a]pyrene-DNA adduct found in cells of experimental animals in which benzo[a]pyrene is known to be carcinogenic following *in vivo* exposure. The response of human and animal cells to inducers and inhibitors of benzo[a]pyrene metabolism is also qualitatively similar (5,6,8). These findings indicate a remarkable qualitative similarity in the response of animal and human tissues to carcinogens." (Harris, S. 3)

Dr. Harris concluded:

"These assays will aid in the qualitative, but not as yet quantitative, assessment of the carcinogenicity of a chemical. Since studies with tissues from both human and animal models can be conducted in parallel, direct comparison can be made with the tissues maintained in the same controlled experimental setting." (Harris, S. 7)

Dr. Trump also cited specific examples of the similarities in metabolism between animal and human tissues in his written testimony (S. 5–12) and concluded in his summary:

"3. *Experimental exposure to human lung tissues* (maintained as xenografts in immune-deficient mice) *to carcinogens results in a sequential development of early lesions exactly resembling that seen in specimens from patients with lung cancer and in hamsters treated with BP–Fe_2O_3.*

"4. *Both human and animal tissues metabolize chemical carcinogens to mutagenic metabolites which bind to DNA . . .*

". . . In general, these results provide strong support for the use of experimental animal systems in identifying carcinogens which pose a risk to humans. In addition, tissue culture systems are proving to be excellent tools for the identification of carcinogens and mutagens, and for study of mechanisms of carcinogenesis." (Trump, S. 13, emphases in original)

What Dr. Harris said explicitly and Dr. Trump implied in these statements is that they have found qualitative similarities between individuals and between different species, while quantitatively the differences may be extensive. For example, Dr. Harris described a wide range of inter-individual variation in the levels of carcinogen-DNA adducts formed, and in the activity of the enzymes responsible for metabolism (S. 3–4). He also described intraspecies differences:

"Intraspecies or strain differences in oncogenic susceptibility have also been found and in some cases linked to the genetically-determined metabolism of the chemical procarcinogen. The carcinogenicity of polynuclear aromatic hydrocarbons, such as benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene and 3-methylcholanthrene, shows a positive correlation with aryl hydrocarbon hydroxylase activity (15); this is one of the enzymes necessary for the metabolic activation of these chemical carcinogens. In a second example, the incidence of colonic carcinomas caused by 1,2-diethylhydrazine varies markedly among strains of mice. These differences in susceptibility to 1,2-diethylhydrazine are genetically determined in the form of dominant inheritance (28). The possible metabolic basis for this observation is currently being investigated in my laboratory." (Harris, S. 5–6)

Dr. Saffiotti also recognized this:

"Metabolic pathways of carcinogen activation do indeed change quantitatively from species to species and even with major dose level changes, but the evidence is that the changes are in the relative proportions of different metabolites rather than in their abrupt disappearance at fixed levels. Many chemical agents, both endogenous and exogenous, can alter the enzymatic systems which control carcinogen activation, for example concurrent exposures to other carcinogens." (Saffiotti, S. 12–13)

In a paper submitted by Dr. Harris, the present limitations of this technique are expressed:

"Man is genetically a heterogeneous population, and pharmacogenetic studies in identical and fraternal twins have shown that interindividual variation in drug metabolism is greater than intraindividual variation (Vessel, 1971). As noted above, there is marked variation among individuals in their ability to metabolize at least one class of chemical carcinogens, polynuclear aromatic hydrocarbons. Whether or not the intraindividual variation of carcinogen metabolism due to exogenous agents, e.g., tobacco smoke, is either more or less than interindividual variation determined by genetic differences is unknown. However, these genetic differences in the metabolic activation of chemical procarcinogens such as benzo[a]pyrene may be a very important host determinant in an individual's risk of developing cancer. While extensive indirect data supporting this hypothesis linking metabolism and susceptibility has accumulated in studies using cells in culture and experimental animals (Weisburger, 1973; Heidelberger, 1975) it has not yet been adequately tested in man. One problem has been the lack of information concerning the metabolic pathways of chemical carcinogens in human target tissues; experimental models using human tissues should help correct this deficiency." (Harris, 1977, p. 399; Exhibit 1 to Harris Statement)

Dr. Trump also discussed some of the limitations of these techniques:

"Since various species of animals are known to differ in the way in which they metabolize foreign compounds, it is obvious that differences could exist between the metabolism occurring in man and that occurring in other animals such as the rodent. For this reason, validation of the results from experimental models is difficult and extrapolation of animal data to man requires assumptions which cannot be verified without more detailed knowledge of the metabolism of carcinogens in the human than is presently available." (Trump, S. 3)

He concluded as follows:

"There is great variability (up to 75-fold) between individuals in the ability of their tissues to bind mutagenic metabolites to DNA. *This variability appears to reflect inter-individual variability in susceptibility to chemical carcinogenesis."* (Trump, S. 13, emphases in original)

(c) *Positive evidence is easier to obtain than negative.* A great deal of the testimony reviewed above has discussed the uncertainties of establishing metabolic and pharmacokinetic differences between humans and animals. An additional uncertainty lies in the attempt to establish that a compound found to be carcinogenic in animals is not metabolized via a similar pathway to the identical ultimate carcinogen. Establishing such a negative finding is particularly difficult due the complicating variables discussed above. A positive finding, however, would stand on its merits and would justify a qualitative inference of carcinogenic risks. Dr. Peter Goldman (Harvard Univ.) expressed this opinion clearly:

"Well, that is right, because a positive, if confirmed, is there whereas a negative, it could always mean that something was not really quite right and change the conditions a little bit, one could get it." (Goldman, Tr. 4482)

(3). Can specific procedures or criteria for the use of metabolic and pharmacokinetic information be laid down on the basis of our present knowledge?

Very few committee reports and research papers have suggested specific procedures for using pharmacokinetic and metabolic information in the evaluation of potential carcinogenic risk for humans. The Food and Drug Administration in publishing *Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Food Producing Animals* has proposed a procedure for the use of metabolic studies:

"C. COMPARATIVE METABOLISM STUDY TO AID IN ASSESSING CARCINOGENCITY OF INTRACTABLE RESIDUES

"1. Sponsored compound always tested: Rationale and procedure. When it is determined that a sponsored compound has the potential to contaminate edible tissues with residues whose consumption may pose a human risk of carcinogenesis, the sponsored compound itself shall always be tested for carcinogenesis. Residues are selected for testing according to those criteria already

discussed in paragraph III.B., but there are overriding reasons for testing the sponsored compound, even if it is not detected as a residue. Metabolic transformation or nonenzymatic degradation of a sponsored compound can lead to a number of tissue residues which cannot be obtained (either by isolation or synthesis) in sufficient amounts for carcinogenicity testing (such residues are herein and in the regulation referred to as "intractable residues"). Testing the sponsored compound itself therefore provides one experimental means for acquiring data on the carcinogenic potential of such residues.

"Although the dominant criterion for selecting test animal species or strains for chronic toxicity testing will be the degree to which a species or strain models man, the application of a secondary criterion for selection can provide a means for addressing the problem of intractable residues. Specifically, selection of test animals can also be based on comparative metabolism data (target animal and test animal) which can be used to determine the extent to which particular species or strains, by virtue of the way they metabolically convert the sponsored compound, will be exposed during testing to the same complement of residues expected in tissues derived from target, animals.

"For example, if a metabolite detected as a residue in edible tissues of the target animal is determined to be toxicologically important, the petitioner will be asked to pursue isolation or synthesis of the compound for toxicity testing purposes. If all attempts at this fail, then the comparative metabolism approach is available if a potential test animal species is shown to produce the same metabolite when it is administered the sponsored compound. In this way, there is some degree of assurance that the toxicity test of the sponsored compound also provides some estimate of the toxicity of the intractable metabolite. Because human food could be contaminated with the intractable metabolite, such a test provides a practical approach to a complex and important issue.

"This construct has been included in the final regulations in response to comments that all metabolites ought to be ignored (which the Commissioner concludes is neither legally nor scientifically acceptable) or that all metabolites must be isolated and independently tested (which is not technologically possible).

"2. Selection of residues for chronic toxicity testing. On the basis of all of the studies described above, the Commissioner will select those residues, in addition to the sponsored compound, that require chronic toxicity testing." (42 FR 10417)

EPA recently proposed a similar procedure in its *Proposed Guidelines for Registering Pesticides in the U.S.; Hazard Evaluation: Humans and Domestic Animals:*

"163.85–1 General metabolism studies.

"(a) Purpose. A general metabolism study is required for the following major purposes:

(1) To identify and to the extent possible, quantify significant metabolites;

(2) To determine any possible bioaccumulation and/or bioretention of the test substance and/or metabolites;

(3) To determine pesticide absorption as a function of dose;

(4) To characterize route(s) and rate(s) of pesticide excretion;

(5) To relate pesticide absorption to the duration of exposure of the animal; and

(6) To obtain an estimate of binding of the test substances and/or its metabolites by target macromolecules in potential target organs.

"(b) When required. Data from a general metabolism study are required to support the registration of each formulated product which requires a chronic feeding study or an oncogenicity study, in accordance with § 163.83–1 and § 163.83–2." (43 FR 37394; Exhibit 218)

The Scientific Committee of the Food Safety Council described a detailed method for utilizing metabolic and pharmacokinetic data "to be used in planning both the strategy and tactics of the approaches to safety evaluation":

"The study of the metabolism and pharmacokinetics of an ingested substance is carried out for the following purposes:

"A. To gain a general understanding of the absorption, biotransformation, disposition, and elimination of the ingested substance after a single dose and after repeated doses.

"B. To provide information about the rate at which these processes occur, and the temporal relationships between dose and tissue levels reached so that the following information may be derived:

1. Whether steady-state tissue concentrations are achieved.

2. Time required to achieve a steady state with a particular dosage regimen.

3. Total metabolite load at the steady state.

4. How the metabolic and pharmacokinetic characteristics change with time, dose, and dosage regimen.

5. Under what circumstances the metabolic and/or excretory systems become overloaded. This need implies that pharmacokinetic studies should bracket the toxic doses for the species investigated, i.e., should cover "normal" metabolism as well as metabolism under extreme stress levels of the compound.

"In accordance with this separation in the degrees of required sophistication, the study of metabolism and pharmacokinetics may be divided into two stages as follows:

"Stage I—scheduled to follow a series of acute toxicity and mutagenicity evaluations and to precede subchronic tests. The purpose is to provide a general overview of the fate of an ingested substance in the body. The information obtained should help to determine the doses to be used, to arrive at the method and frequency of administration, species to be selected, and determine the duration of the subchronic studies in animals.

"Stage II—follows a decision to embark upon long-term studies and involves a more detailed examination intended to yield the central information for planning the dose regimen and other features of the long-term investigations.

"Stage I aims at fulfilling objective A above and, to a limited extend, providing some of the items of information (for example, B.1. and 2.) listed under objective B. by the time stage II is undertaken, the main emphasis will be directed to the outstanding questions arising from the findings to date, as they relate to objective A., but more particularly to objective B. *Any attempt to specify precisely the nature of the investigations and their protocols in stages I and II would be contrary to the general policy laid down for this report, namely the maintenance of flexibility to permit the overall approach to be tailored to the particular compound under investigation.*

"The relevance of these considerations is exemplified by the description below of a wide range of preliminary investigations, as well as ancillary metabolic studies that can be carried out in vitro. Judicious selection of appropriate experimental procedures will often prove helpful. To attempt to weave all these approaches into a rigid sequence of mandated studies would result in much wasted effort; conversely, to omit them altogether would deprive the innovative investigator of valuable techniques. (Food Safety Council, 1978, p. 65–66; Hearing Exhibit 227, emphasis added.)

It should be recognized, again, that all three of these procedures were proposed as part of a battery of tests designed to establish the safety of a tested compound. These elaborate series of tests were not recommended as part of a procedure to interpret positive results in animal tests, and there was no showing that any of them would be crucial or even important in such interpretation.

The NAS Committee on Safe Drinking Water did not suggest any method for using pharmacokinetic and metabolic data but did make recommendations as follows:

"Research must be supported to develop an understanding of the mechanisms by which water pollutants produce toxic effects. This includes pharmacokinetics, toxication-detoxication mechanisms, and biochemical and pathological mechanisms of action.

"Estimates of margin of safety can be made more precisely and rationally as more is known about what happens to a chemical in the body and what the chemical or its metabolites do to the body. The results of such research also are necessary to develop rapid, inexpensive, accurate screening tests for various critical forms of toxicity.

"It is recognized that much of this research is going on, but the Committee is convinced that more must be done. In protecting the population of the United States from environmental pollution there is no more important or potentially productive effort than the support of this kind of research. Since these studies are long-term in nature and must be closely coupled to basic biomedical research, they should be supported primarily by research rather than regulatory agencies." (NAS, 1977a, p. 58; Exhibit I to Rall Statement)

During the hearing, only two witnesses provided OSHA with

documented examples of how to use metabolic and pharmacokinetic data. Dr. Perry Gehring (Dow Chemical) was one. Dr. Gehring's work, however, was concerned primarily with identification of dose-dependent changes in metabolism and pharmacokinetics. Its relevance to this regulation has been discussed elsewhere in this Preamble in relation to the hypothesis of threshold resulting from "metabolic over-loading" (See section V.D. 3. *Testing at High Doses).*

Dr. Raymond Yang (Carnegie-Mellon) suggested a specific method, "Comparative Metabolic Profile Analysis", which has been previously described. Dr. Yang recommended that this method may prove useful in selecting a suitable species for chronic toxicity testing:

"For those chemicals which demonstrate carcinogenic properties toward one or more animal species but for which there is no available information regarding human response, this approach may provide valuable information concerning metabolic similarity or differences between the tested species and man. Thus the extrapolation of results of animal experiments to man could be done on a more scientific basis.

"For those chemicals whose chronic toxicities have never been established, the application of this approach may assist in the rational selection of animal models for chronic toxicity studies based on their metabolic similarity to man. This might obviate conducting unnecessary, long-term animal toxicity studies in metabolically unsuitable species." (Yang, S. 4–5)

A recent article by J. F. Young and J. F. Holson of the National Center for Toxicological Research presented the following conclusions and recommendations:

"In conclusion, the following recommendations for designing and evaluating pharmacodynamic studies are made:

"1. Initiate the pharmacokinetic studies early in the testing sequence so that the results can be used to help evaluate the toxicity as well as to design further tests.

"2. Use the following guidelines for the pharmacodynamic studies:

(a) Use i.v. dosing initially.

(b) Obtain serial blood samples from maternal animals prior to sacrifice and measurement in embryos.

(c) Do not combine blood data from different animals for analysis as a group, but perform the pharmacokinetic analysis on each individually.

(d) Check for dose-independent or dose-dependent pharmacokinetics.

(e) Choose comparable gestation times and stages when comparing species.

(f) Select doses so that dosimetry is constant across species.

(g) Validate your model by increasing or decreasing the dosimetry." (Young and Holson, 1978, p. 185–186)

All of these recommendations and suggestions address the problem of designing or selecting a species for testing which is "comparable" to man with respect to available metabolic or pharmacokinetic data. No specific recommendations were made which could assist OSHA to interpret or evaluate the reported results of bioassays conducted in the past in assessing potential carcinogenic risk for humans.

c. OSHA's Conclusions

On detailed review of the scientific evidence in the record, OSHA draws the following conclusions:

1. Several expert committees and reviewing bodies which have reported since 1977 have recommended that studies of metabolism and pharmacokinetics should be incorporated into procedures for safety testing of chemicals.

2. Recommendations for the use of information on metabolism and pharmacokinetics have been limited to recommendations for its use in planning further tests, or for quantitative interpretation of dose-response relationships, or both.

3. No serious scientific arguments were presented that would indicate that information on metabolism and pharmacokinetics is essential for retrospective interpretation of tests carried out in the past.

4. Information on metabolism and pharmacokinetics of carcinogens is generally deficient even for experimental animals and is especially deficient for humans. Tissue culture techniques afford some promise for future use, but are not sufficiently well developed for routine use at the present time.

5. To rebut the *qualitative* presumption that a chemical found carcinogenic in animals poses a risk to exposed humans, it would at least be necessary to show (a) that the metabolite identified as the ultimate carcinogen in animals is not produced in human tissues, and (b) that other metabolites of such a substance produced in human tissues are not carcinogenic. OSHA does not believe that such information is available for any carcinogen, and indeed OSHA believes that such information is unlikely to become available because of the wide variability in metabolic differences between different tissues and between individuals in the population.

6. Although information in pharmacokinetics is theoretically important for quantitative risk assessment, there is so much variability among individuals that the principal consequence of considering pharmacokinetic data is to increase the range of uncertainty in such estimates.

OSHA concludes, based on the Record, that, in general, for the purposes of negating the identification or classification of potential occupational carcinogens, information on metabolism and pharmacokinetics is of extremely little practical value at the present time. For the reasons stated above, OSHA will not require information on metabolism or pharmacokinetics as part of its procedures for identifying and classifying potential occupational carcinogens, and will not ordinarily consider such evidence unless a strong showing is made that it would be sufficient to rebut the general inference that a substance which gives positive results in carcinogenesis bioassays in one species would pose a potential risk to exposed workers. Such evidence will be considered, if the following minimum criteria which have been selected on the basis of a detailed review of the evidence in the Record are met.

As general background to the criteria specified below, OSHA points out that the only way in which metabolic data would suffice to show that a substance which induces cancer in animals would not pose any risk to humans would be to prove that it did so via a metabolite that is only produced in the animal species and is not produced in humans under any circumstances (see, generally, the analysis in sections 1 and 2(c) above). Thus the absolute minimum criteria for the consideration of such data would appear to be that the metabolites of the substance must be completely known in both the experimental animal species and in humans. Therefore, OSHA's first two specific criteria are that a complete metabolic profile, including identities of trace metabolites, must be presented for both the experimental animal species and for humans.

Thus, § 1990.144(c) provides:

(c) Metabolic differences.

Arguments that differences in metabolic profiles can be used to demonstrate that a chemical found positive in an experimental study in a mammalian species would pose no potential carcinogenic risk to exposed workers will be considered by the Secretary only if the evidence presented for the specific substance subject to the rulemaking meets the following criteria:

Criteria. (i) A complete metabolic profile, including identities of trace metabolites, is presented for the experimental animal species;

(ii) A complete metabolic profile, including identities of trace metabolites, is available for a human population group representative of those who are occupationally exposed;

(iii) Documented evidence is provided for ascribing the carcinogenic activity of the substance in the test animal species to metabolite(s) produced only in that species and not in humans; and

(iv) Documented evidence is provided to show that other metabolites produced also in humans have been adequately tested and have not been shown to be carcinogenic.

In presenting these criteria, OSHA is not recommending or endorsing deliberate human experimentation. OSHA anticipates that in some cases data on metabolism in humans may be available from studies of workers already exposed, or from tissue culture studies. Whatever the source of the data, the completeness of the metabolic profiles, and the completeness and representativeness of the samples from which data are derived, will be issues to be explored thoroughly.

In the event that metabolic profiles for the experimental animals and humans are qualitatively different, OSHA will require a reasonable showing that the carcinogenicity of the substance in animals can be linked clearly with one or more metabolites which are produced only in the animals. General arguments that the existence of these metabolites "weakens" or "might" negate the inference of potential hazard to humans are of little scientific or evidentiary value and will not be considered. Instead OSHA will impose these two specific minimum requirements: (i) some tangible evidence must be presented to indicate that the animal metabolite is either the ultimate carcinogen or is the indispensable step in the carcinogenic process (e.g., evidence of mutagenicity of covalent binding to DNA); and (ii) some tangible evidence must be presented that the other metabolites which are produced in humans are not also carcinogenic. OSHA believes these criteria are reasonable. OSHA's intent is to ensure that evidence will be considered if it provides reasonable grounds for establishing that metabolic differences are truly significant in the process of identifying carcinogens, while preventing a waste of time or resources on discussion of evidence that is irrelevant or whose interpretation is speculative or hypothetical.

Finally, it is important to note the use of metabolic data in identifying potential carcinogens. An extremely important general point which was brought out in the scientific evidence on metabolism presented in the Record is that most "carcinogens" require metabolic activation before they can interact with genetic material and initiate the process of carcinogenesis. In commonly used scientific terminology, the substances administered to experimental animals are referred to as "procarcinogens" and are metabolized within the body one or more times to yield "proximate carcinogens" and "ultimate carcinogens." The "ultimate carcinogens" are reactive, often electrophilic, compounds which react with DNA or other macromolecules in the cell and are believed thereby to initiate the process which ultimately leads to cancer. (See, in general, the statements and exhibits of Drs. Upton, Saffiotti, Rall, Fishbein, Roe, and Kotin; for detailed testimony on the mechanisms of metabolic activation see the statements and exhibits of Drs. Hart, Trump, and Curtis Harris).

Apart from the intrinsic scientific interest of these recent findings, they have an important practical consequence, in that the definition of "carcinogen" has to be broad enough to include "procarcinogens" and "proximate carcinogens" as well as "ultimate carcinogens." In a narrow technical sense, only "ultimate carcinogens" *initiate* cancer. However, since the "ultimate carcinogens" result from the metabolic activation of procarcinogens within the body, the administration of "procarcinogens" to an animal is the original event which leads to this initiation. It is widely understood that procarcinogens are *causes* of cancer in this sense, even though it is now understood that there are frequently intermediate metabolic events in the chain of causation. OSHA's definition of a potential occupational carcinogen as an agent which "causes" an increased incidence of neoplasms is intended to be broad enough to include both procarcinogens and ultimate carcinogens. This usage is in agreement with universal scientific practice, since all the lists of carcinogens proffered at the hearing included agents which require metabolic activation.

Another practical consequence of this scientific knowledge about metabolic activation is that in some circumstances a substance may be identified as a potential carcinogen primarily on the basis of metabolic information. If substance A is known to be metabolized into substance B in the body, and if substance B is known to be carcinogenic on the basis of human or animal studies, OSHA believes that there is a clear scientific inference that substance A should be treated as carcinogenic, whether or not it has been tested directly. OSHA has clarified its definition of potential occupational carcinogen to make this point explicit. Thus, the definition of "Potential occupational carcinogen" 29 CFR 1990.103 now states: "This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals." In practice, this circumstance might arise in several ways. At the simplest level, a substance such as benzidine hydrochloride would be identified as a potential occupational carcinogen because it is known to dissociate to yield benzidine in biological media. Likewise, some benzidine-based dyes would be identified as potential occupational carcinogens if they are shown to be metabolized to yield free benzidine. As another example, organic compounds of such metals as arsenic and nickel would be identified as potential occupational carcinogens if they are shown to be metabolically converted to inorganic compounds of these metals known to be carcinogenic. The issues raised by the metabolic interconversion of inorganic compounds are discussed more fully in Section VII below, *Structural Similarities to Known Carcinogens.*

For the purpose of applying this provision of the definition, OSHA will, where appropriate, scientifically evaluate the results of experimental studies of the metabolism of substances subject to regulation under this part. The basis for the conduct of metabolic studies in mammals and in human tissues was presented in the testimony of Dr. Yang, Dr. Trump, and Dr. Curtis Harris among others. In general, metabolites formed in any species of mammal will be considered relevant to the evaluation of potential human risks, although OSHA will consider evidence proffered on interspecific differences in metabolism if such evidence meets the criteria specified in § 1990.144(c). Metabolites formed by non-mammalian species (other than mammalian gut flora in vivo) will not be considered relevant. In general, the results of metabolism studies conducted in mammals in vivo will be preferred, but the results of in vitro metabolism studies conducted with mammalian tissues or fractions thereof will be used if they are found to be valid and relevant upon scientific evaluation. The presence of carcinogenic or mutagenic metabolites in the urine or body fluids of exposed workers will be considered *prima facie* evidence of hazard.

VI. SHORT TERM OR IN VITRO TESTS FOR CARCINOGENESIS

A. OSHA's Proposal

In the preamble to the proposed regulation, OSHA briefly discussed the advantages and the limitations of short-term tests:

"OSHA is aware that short-term and *in vitro* tests for carcinogens are being developed rapidly, take a few weeks at most to complete and yet examine the capacity of a substance to cause mutagenicity, other genetic alterations or neoplastic transformation. Reliance upon the short-term mutagenic tests is based upon the assumption that cancer can be related to genetic alterations and that, therefore, detection of such changes is indicative that such a substance may have carcinogenic potential. Mutagenesis tests are very useful as screening tests because they can be conducted quickly and inexpensively. In addition, short term tests have been developed to test the ability of a substance to induce neoplastic transformation of cells that are cultured *in vitro*.

"Short term tests use a variety of biological systems, such as bacteria, yeast and mammalian cells. These methods are in various stages of development and some of these methods have been more extensively utilized than other ones. To date, the most widely used method appears to be the Salmonella, or Ames, test. This method utilizes several specially constructed strains of Salmonella bacteria to detect mutagenic changes. Rat (or human) liver extracts are used to activate the mutagenic form of the substance being tested. However, although the correlation between positive short term tests and animal carcinogenicity may be good, the number of validation studies is still small." (42 FR 54167)

Being aware of the limitations of these tests, OSHA agreed with the judgment set down by the NCAB Subcommittee:

"A major practical limitation in the bioassay of potential carcinogens is the large number of test animals and the long duration required to obtain results. A number of short-term or in vitro tests are currently under development and appear promising. These include assays for: the induction of DNA damage and repair; mutagenesis in bacteria, yeast, *Drosophila melanogaster*, or in mammalian somatic cell cultures; and neoplastic transformation of mammalian cells in culture. Other assays that have been employed include the dominant lethal test and studies of chromosomal damage. The latter two tests suffer from the fact that they are frequently non-specific and/or difficult to quantify. Of the various short-term tests, the Ames *Salmonella* mutagenesis system has been studied the most extensively. Tests based on other in vitro approaches are also being developed.

"The intelligent application and interpretation of the in vitro tests must also take into account species variations in factors related to the pharmacologic distribution and metabolism of the parent compound as well as possible species differences in macromolecular repair and host defense mechanisms. A number of approaches addressed to the metabolic aspects are now available, including "host-mediated" mutagenesis assays; the assay of urine and other biologic fluids taken from animals or humans receiving the test compound; the addition of microsomal enzymes and co-factors to the assay system; and the inclusion of specific cells in the assay.

"At present, none of the short-term tests can be used to establish whether a compound will or will not be carcinogenic in human or experimental animals. Positive results obtained in these systems suggest extensive testing of the agent in long-term animal bioassays, particularly if there are other reasons for testing. Negative results in a short-term test, however, do not establish the safety of the agent.

"This Subcommittee is enthusiastic about the possible future use of in vitro tests as part of a screening system for potential carcinogens and believes that their further development and validation deserve high priority." (NCAB Report, 1977, p. 462–463; Exhibit B to Weinstein Statement)

OSHA did not propose to use any short-term tests as the *sole* basis for the identification of potential carcinogens. Citing the FDA decision to ban chloroform, however, OSHA did propose to use short-term tests, when adequately performed, as confirmatory evidence to support results from animal bioassays:

"In particular OSHA proposes that the combination of positive results in short term tests and a positive result for carcinogenesis in a single bioassay in a mammalian test species would provide sufficient evidence for classifying a substance as a Category I toxic material." (42 FR 54168)

OSHA was, therefore, primarily concerned with using short term tests to *confirm* results provided by animal bioassays and not as a *substitute* for bioassay data.

B. The Public Response and OSHA's Evaluation

First, some participants commented that OSHA should not use short term tests as the sole basis for determining the carcinogenicity of a substance, and that substituting short term tests for an animal bioassay was inappropriate. For example, NACA, in discussing why short term tests are not sufficient to place a substance in Category I, commented:

". . . the term short term tests, which is not defined in the proposed rule, is assumed to refer to short term tests for mutagenicity. These tests may be capable of detecting mutagenic effects, but not carcinogenic effects. . . . Mutagenicity testing is not an accepted method of assessing carcinogenic risk to man." (NACA, S. 47–48)

Mobay Chemicals commented:

"We do not feel a 'short-term' or *in vitro* test, or a battery of these tests, can, at the present time, be given significance equal to that of a well conducted long-term animal study in considering the potential carcinogenicity of a substance." (Mobay, S. 27)

Gulf Oil Chemicals commented:

"OSHA proposes to give equal weight, in the regulatory process, to tests in two mammalian species, and in one mammalian species and 'short-term tests' (which are enumerated in the OSHA proposal). 'Short-term tests' used in this manner have not been shown to be uniformly valid predicters of human carcinogenic potential and should not be given equal weight with mammalian testing." (Gulf Oil Chemicals Co., S. 2)

Ciba Geigy commented:

"While we agree that the short-term *in vitro* assays are acceptable as a gross screening method appropriate to determine the need for more sophisticated *in vitro* or *in vivo* tests, to use them as a definite indicator of carcinogenicity in humans or animals is inappropriate at this time." (Ciba Geigy, S. 7)

Other witnesses whose testimony reflected this view as well were Dr. Alonzo Lawrence (Koppers), Tr. 7778–7779; Dr. Rulon Rawson (Univ. of Texas), Tr. 4420; Dr. Mitchell Zavon (Hooker Chemical), Tr. 5378; and Dr. Harry Skalsky (Reynolds Aluminum), Tr. 7592–7593.

Second, a number of witnesses and comments addressed the role of short-term tests in identifying and classifying carcinogenic potential for humans. Several broad issues were raised which will be discussed in depth below:

1. How can short-term tests be used in predicting potential carcinogenic risks for humans?
2. What short-term tests are currently available and how much weight should be placed on each?
3. What is the current status of validation for each?
4. How well do short-term tests predict carcinogenesis?
5. What degree of confidence do short-term tests add to the results of animal bioassays in the evaluation of carcinogenic risks for humans?
6. Can a battery of short-term tests be developed which would provide reasonable predictions of carcinogenic activity, and if so, what criteria should be met by such a battery?
7. Would the regulation of carcinogens which are also mutagens provide additional benefits by reducing mutagenic hazards?

In analyzing these issues, as pointed out below, OSHA places primary weight on the testimony of witnesses and participants who documented their statements and who, from their experience in working with short term tests, are considered experts in this field. These included Dr. Joyce McCann (University of California); Dr. Matthew Meselson (Harvard University); Dr. Benjamin Trump (University of Maryland); Dr. Curtis Harris (NCI); Dr. Lawrence Fishbein (NCTR); Dr. Ronald Hart (Ohio State Univ.); and Dr. David Brusick (AIHC).

1. How Can Short-Term Tests Best Be Used in Predicting Potential Carcinogenic Risks for Humans?

Many witnesses addressed the question of what role short term tests should have in regulatory procedures. However, there was a wide range of comments reflecting substantial disagreement on the extent to which these tests should be used. Some participants claimed that one or more short term tests should be a sufficient basis for regulatory action to begin (EDF, Tr. 6357). Others believed that, at this time, no confidence at all could be placed in these tests until they are further validated. Almost all witnesses agreed, however, that these tests could be applied at least as a screening device for setting priorities in selecting substances for testing in long-term animal bioassays. This spectrum of opinion was similarly reflected in the summary of a workshop conducted by the Chemical Industry Institute of Toxicology (CIIT) entitled—"Strategies for Short-Term Testing for Mutagens/Carcinogens":

"Many new short-term tests have been proposed to predict the mutagenic/carcinogenic activity of chemicals, and it would appear that these tests have the potential of revolutionizing this area of toxicology. However, there currently exists a wide range of opinion as to the usefulness of the short-term tests. On the one hand, some investigators feel that these assays are so well developed and validated that they should be adopted by regulatory agencies as a valuable part of the health hazard assessment of chemicals. They believe that the testing procedures and interpretation of results can be rigorously defined in regulations so that governmental administrators and lawyers can fairly and usefully apply such laws. On the other hand, others see the tests as having some value, but being capable of producing misleading information. They consider it doubtful, at best, that the ability of a chemical to induce mutagenic effects in bacteria could in any way realistically predict the role such a chemical might play in the complex process of carcinogencsis in man. They point out that for many proposed short-term assays experimental details have not been well defined, important factors in the tests, such as the metabolic activation system, are poorly understood and lack standardization, and most tests have not been evaluated with reasonable numbers of compounds of known mutagenicity/carcinogenicity." (Golberg, S. 5)

There were, however, a number of recommendations to OSHA regarding how best to use these tests. Dr. David Rall (Director, NIEHS) gave a clear, concise description of how short-term tests would be useful to confirm results from long-term animal bioassays:

"There is no question that positive results in short-term tests (such as the Ames test, induction of unscheduled DNA repair, or malignant cell transformation *in vitro*) add to the confidence that one would have in a single positive animal test. This is not to say that these short-term tests are *equivalent* to lifetime bioassays in rodents: it merely reflects the fact that most carcinogens give positive results in short-term tests. Hence, if there is any reluctance to accept the result of a single animal bioassay, positive results in short-term tests would add sufficient evidence to overcome this reluctance. Certainly, it seems reasonable to use them in this way rather than to demand a second lifetime test in a rodent, which would be lengthy and expensive." (Rall, S. 14)

Dr. Robert Squire (Johns Hopkins University) expressed a similar opinion:

"These tests should also be evaluated when weighing the potential carcinogenic risk of certain chemicals, because they may provide evidence that corroborates animal test results." (Squire, S. 9)

Dr. Arthur Upton (Director, NCI) commented in his oral testimony that short term tests may be useful as a prescreen in the selection of chemicals for long-term testing or to help isolate the ultimate carcinogen or "substance in question":

"To my knowledge, we do not yet have adequate understanding of the predictive value of short-term tests to rely on them solely as a basis for regulatory decisions. And for that reason, I think that those working in the field today view them as useful in several ways. One, indeed, as a shortcut pre-screen, if you will, in the selection of compounds for longer-term testing. And secondly, in providing additional evidence as to the action of the compound in question in the cellular system. When we put a chemical into an animal and eventually see the tumor result, as I mentioned in my opening statement, we can envisage that a complicated series of chain reactions has taken place between the introduction of the substance, final appearance of the tumor. The short-term test may help us in determining that the substance in question is, in fact, genotoxic, is capable of attacking the genes of the cell. We know there is a very high correlation between genotoxicity or mutagenicity and carcinogenicity." (Upton, Tr. 289–290)

Dr. Lawrence Fishbein (NCTR) also expressed his opinion on the value of data from mutagenic assays in setting priorities:

"And if shown to be positive in the more applicable ones, those where there are larger data bases, such as the Ames, et cetera, and its importance is such that considering that animal bioassays are expensive and time-consuming, that this would help prioritize the selection." (Fishbein, Tr. 1869)

Dr. Maurice Johnson (B. F. Goodrich: AIHC Alternatives Panel) suggested that positive results from short-term tests may serve as a warning of possible carcinogenic hazard to employees working with such substances:

". . . there would be short-term in vitro tests such as the Ames test, mouse lymphoma, mammalian cell transformation, DNA damage which are useful carcinogenic screening tests. While there are limitations to such tests, we believe that they are useful warnings of a possible carcinogenic hazard. Positive test results should be reported to the affected workers and to the proper governmental agencies. OSHA should publish the results of these in vitro tests and issue an interim work practice standard. This could be in the form of a model standard. The employer should ensure that these work practices are initiated, and these might include providing facilities for washing and showering upon leaving the work area, providing eating areas away from possible exposure areas, and maintaining good cleanup of spills.

"The employer should then conduct a hazard evaluation to determine all areas where human exposure to the substance may occur. In addition, measurement techniques which will aid in determining the extent of the exposure to the substances should be developed. Engineering measures to reduce exposure should be initiated.

"Animal studies should be initiated to determine in vivo carcinogenicity and the initiation of these studies should be reported." (Johnson, Tr. 4165–4166)

Dr. Johnson went even further and agreed that if after a two year period, no new data were available on a substance found positive in a short term test, then it would be appropriate for OSHA to require the implementation of engineering controls (Johnson, Tr. 4175).

Dr. David Brusick (AIHC) provided detailed evidence for another use of short-term tests. Dr. Brusick discussed how these tests are useful in the understanding of the mechanisms of carcinogenesis at the molecular level and in defining the potential of a substance to be carcinogenic:

"Although the spectrum of submammalian and in vitro assays is broad, the objective of these as applied to chemical carcinogenesis is similar; and that is, to identify chemicals which have the capability of inducing DNA alterations or morphologically transformed cells. This information is then used to define the genetic/carcinogenic potential of the chemical." (Brusick, S. 8)

Dr. Brusick then went on to suggest the following roles for the use of short-term tests (STT):

"(a) Results from a battery of STT can be used to identify genetic/carcinogenic potential if all or most of the responses are unequivocally positive. This identification cannot be equated with a definitive classification of the chemical as an animal carcinogen.

"(b) Results from STT can be used to identify potential mutagens/carcinogens in situations where insufficient quantities of the test material can be produced or collected to perform large scale rodent bioassays; for example, concentrated environmental air or

water samples, treated crop residues' samples or tissue residue samples from treated fish, poultry, or mammals consumed by humans.

"(c) Results from STT can be used to design rodent bioassay studies along the following lines; species selection based on data from in vitro activation studies of chemical bioactivation to its active form, and identification of susceptible target tissues based again on comparative levels of in vitro bioactivation. The results of STT would be useful in designing the size of the confirmatory rodent bioassay. The number of dose levels and animals per group might vary depending on this preliminary information.

"(d) STT should be used to develop working hypotheses for the concepts of mechanism of cancer induction, threshold levels and species extrapolation. These hypotheses can provide the framework upon which specific resolution of these problems can be made using appropriate animal assays." (Brusick, S. 15–16)

Other witnesses who also commented that short-term tests might be useful in the understanding of the mechanisms of carcinogenesis were Dr. Benjamin Trump (University of Maryland), Dr. Curtis Harris (NCI) and Dr. Umberto Saffiotti (NCI) (S. 37). Dr. Trump described how his *in vitro* test system could be useful in this manner:

"And the main thing about our systems is that by culturing organized tissues, you can not only do short-term effects, like examine for mutagenic metabolites using either bacterial or mammalian cell system, but you can also look over the long run and study the development of actual lesions in this organized tissue and compare those with what occurs in the human bronchus or human pancreas . . .

". . . or the animal model, and that is what is the most exciting thing to us, being mainly interested in mechanisms. And as was mentioned, it is very encouraging that we are able to take benzpyrene, MNNG, DMBA, and produce in the test tube in organized tissues what we consider to be premalignant epithelial lesions or even carcinomas in situ morphologically in the nude mice that are being used to graph these tissues so transformed morphologically to examine for tumorigenesis." (Trump, Tr. 1980–1982)

Dr. Harris commented:

"Studies of the interactions of chemicals with cultured human tissues and cells can now supplement the carcinogenesis data from experimental animals. Short-term assays with human material described above focus on the interaction of chemicals with DNA, i.e., formation of adducts and induction of mutations. DNA repair synthesis and perhaps increased sister chromatid exchanges in human cells exposed to chemicals are other measures of this interaction which may also prove to be useful as short-term tests. These assays will aid in the qualitative, but not as yet quantitative, assessment of the carcinogenicity of a chemical. Since studies with tissues from both human and animal models can be conducted in parallel, direct comparison can be made with the tissues maintained in the same controlled experimental setting.

"The exciting promise of these assays lies in the potential to identify individuals who are highly susceptible to chemical carcinogens in the environment and the workplace. If this promise is fulfilled, increased preventive efforts can be focused on these predisposed individuals." (Harris, S. 7)

Dr. Joyce McCann (Univ. of Calif.) also provided guidance on how short-term tests could best be used. Dr. McCann commented that:

"Current knowledge amply justifies using short-term tests within a regulatory framework aimed at identifying and regulating potential human carcinogens." (McCann, S. 3)

However, Dr. McCann also commented on the caution that must be used in data from non-human sources:

"At the outset, I believe a key point that must be acknowledged is that incorporation of information from any nonhuman source (including animal carcinogenicity tests and short-term tests) into decisions about the potential health hazards of a chemical, injects an element of uncertainty into the decision which cannot completely be removed. The current state of science in this area cannot guarantee that mistakes will not be made. The important point is that the current state of science can guarantee that if mistakes occur (and they may not), the number of mistakes is likely to be very small. Furthermore, because of the seriousness of cancer as a life-threatening, essentially irreversible disease, it is reasonable to admit one's willingness to accept the possibility of some mistakes in attempting to limit human exposure to potentially life-threatening chemicals. The evidence from animal carcinogenicity tests and short-term tests indicates that the most likely mistakes will be in misclassifying substances, especially the weaker carcinogens, as non-carcinogens, rather than in falsely designating substances as carcinogens.

"The few "false positives" that theoretically may occur will be far outweighed by the many human carcinogens that will be correctly identified." (McCann, S. 2–3)

Dr. McCann then provided four specific points of evidence as support for her statement that short-term tests can be used as outlined in the proposed regulation:

"1. When short-term tests are evaluated for their ability to detect known human carcinogens the same way animal carcinogenicity tests are evaluated, they fare equally well with the animal tests with the one exception of diethylstilbestrol (DES)."

* * * * *

"2. Retrospective validation studies comparing results in short-term tests with those from animal carcinogencity tests indicate a very high correlation between the two general methods of detection and suggest that both methods will more often fail to detect carcinogens than they will falsely detect them."

"3. There are an increasing number of examples where short-term tests have accurately predicted the carcinogenic potential of chemicals."

* * * * *

"4. Short-term tests provide information about the potential carcinogenicity of a chemical in humans that cannot be supplied by rodent cancer tests." (McCann, S. 5–9, emphasis omitted)

Dr. McCann concluded by offering an additional suggestion to OSHA:

"In addition to triggering long term cancer tests, ideally I believe that short-term test data from appropriate test batteries should also trigger animal studies to determine if the chemical can reach the germinal tissue or can cross the placental barrier. I hope the time is not too distant when evidence for this, along with positive data from short-term test batteries is sufficient for a Category I type of classficiation for mutagens." (McCann, S. 14)

In addition to these comments, a number of witnesses expressed the opinion that short term tests were useful only as a screening tool. These witnesses included: Dr. Paul Kotin (Johns-Manville), S. 22; Dr. Rulon Rawson (Univ. of Texas), Tr. 4420; Bristol-Myers, S. 2; Dr. Harry Skalsky (Reynolds Aluminum), Tr. 7601–7602; Dr. George Claus (AIHC, Tr. 3512); Dr. Edward Sowinski (Uniroyal Chemicals), (Tr. 8244–8245). Because these statements, however, lacked the specific documentation or scientific review of the available data as did the other witnesses cited above, OSHA places greater weight upon the opinions of these experts.

2. What Short-Term Tests Are Currently Available and How Much Weight Should Be Placed on Each?

Short term tests were defined in the proposed regulation as follows:

"Short-term tests includes, but is not limited to positive results in more than one of the following assays for: (1) the induction of DNA damage and repair; (2) mutagenesis in bacteria, yeast, or *Drosophila melanogaster*; (3) mutagenesis in mammalian somatic cells; (4) mutagenesis in mammalian germinal cells; or (5) positive results in tests for neoplastic transformation of mammalian cells in culture." (42 FR 54184)

There are many short-term tests which can be used to measure the factors listed in the above definition. However, these tests do not all measure the same mutagenic endpoint. In general, chemicals tested in *in vitro* systems may induce changes which affect different levels of biological organization. Changes may occur at the molecular, cellular or multicellular level. A single substance may induce

chromosomal mutations, breakage or rearrangement of parts of chromosomes, point mutations, changes in single genes, or more subtle changes in DNA. No single short term test will measure all of these events. As a result, a substance may produce different results in different tests depending on how its mechanism of action affects DNA or cellular organization.

During the course of the hearing, a large number of short-term tests were described, defined, listed and discussed. The most extensive descriptive list was found in the report of the DHEW Subcommittee on Environmental Mutagenesis in which 35 tests are described. A more workable list of short term tests was found in the OTA report on saccharin. In this study, twelve short term tests were described, nine in full detail:

"1. *Sister Chromatid Exchange (SCE).*—The sister chromatid exchange (SCE) test (134,161) is similar to other cytogenetic procedures in that it measures changes in chromosomal structure. However, it employs a special staining technique to detect subtle changes that do not affect gross chromosomal structure. Classical cytogenetic techniques depend upon such gross changes in structure for detection. In many cases, SCEs have been shown to occur more frequently than gross chromosome aberrations after treatment of cells with chemical mutagens. For this reason, the SCE test may be a more sensitive method than standard cytogenetic procedures for detection of chemicals which have weak cytogenetic activity. The role of SCEs in the generation of mutagenic events in cells has not been proven. But considerable experimental evidence, consistent with the theoretical understanding of how mutations are likely to occur, indicates that events which cause SCEs also can cause mutations. A number of carcinogens and a few noncarcinogens have been tested using the SCE procedure (1,134,161), and the correlation looks promising. However, the method needs to be thoroughly validated to demonstrate its value as a predictor of carcinogenicity and mutagenicity."

* * * * *

"2. *Mutagenesis Tests in Mammalian Cells in Culture.*—Several mutagenesis tests using mammalian cells in culture are in various stages of development and validation. The two used to test saccharin are the mouse lymphona (31) and Chinese hamster ovary (CHO)/HGPRT (130) tests. These methods are similar in that both measure mutations at a specific locus in either mouse lymphoma or CHO cells. Both select mutants that are resistant to either purine (HGPRT test) or pyrimidine (mouse lymphoma test) analogues which, if incorporated into DNA, are lethal to the cell. A mutation at the HGPRT genetic locus in CHO cells makes it impossible for a purine analogue to be incorporated into DNA, and a mutation at the TK genetic locus in mouse lymphoma cells prevents incorporation of certain pyrimidine analogues. Currently, the genetics of the CHO cell line is better defined, but the mouse lymphoma system has been more extensively used for mutagenesis testing. A validation study on the CHO/HGPRT system is in progress, and some results have been published (131). Although the mouse lymphoma test is being used by a number of laboratories and many chemicals have been tested, most of the results have not yet been published."

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"3. *In Vitro Cytogenetic Tests for Chromosome Aberration in Mammalian Cells in Culture.*—Cytogenetic tests measure changes in the morphological structure of chromosomes. A number of different types of structural changes can be produced. Many of these changes are lethal to cells, but some can lead to stable mutagenic changes. Many cytogenetic methods are available, using a variety of cell types from both mammals and humans and using both *in vitro* and *in vivo* procedures. For example, some of the most frequently used *in vivo* methods measure changes in chromosome structure in bone marrow cells, peripheral lymphocytes, or spermatocytes in animals. *In vitro* human peripheral lymphocytes are often used, as well as a wide variety of cell lines from both humans and animals."

* * * * *

"4. *The Salmonella/Ames Test.*—This test is currently the most widely used of the short-term tests. A large number of known carcinogens have been tested and shown to be mutagens in this system (96,97,139, 155,163). The method is very efficient for detection of organic chemical carcinogens (about 90 percent of those tested can be detected), but it does not detect all classes of carcinogens with equal efficiency. For example, metals, some chlorinated hydrocarbons, and the hydrazines are poorly detected.

"The procedure uses several specially constructed strains of the bacterium *Salmonella typhimurium*. These strains contain different mutations that inactivate the genes necessary for the synthesis of the amino acid histidine, and as a result that bacteria cannot grow unless this amino acid is added to the growth medium. The test is carried out by exposing the bacteria to the chemical to be tested and measuring the number of bacterial colonies that are able to grow in the absence of histidine. Each such bacterial colony is the product of a mutational event. A correlation between increasing dosage of a chemical and increasing numbers of colonies shows the chemical to be mutagenic. The method also incorporates rodent (or human) liver extracts into the assay mixture to provide 'activating enzymes,' which are necessary to metabolize some carcinogens to their active forms."

* * * * *

"5. *Mitotic Recombination in Yeast.*—A number of different types of genetic events can be assayed in yeast. The most widely used assays for testing carcinogens and mutagens are those that measure mitotic recombinations (194). This process involves breaking and rejoining parts of homologous chromosomes and can lead to changes in the genetic characteristics of the organisms. Mitotic recombination can result in chromosomal mutations that affect large numbers of genes, as compared to point mutations, which affect single genes. The basic molecular processes involved in these two mutagenic events are most likely related because chemicals that induce mitotic recombination, almost without exception, also cause point mutations. The yeast that has been most commonly used to detect mitotic recombination events is *Saccharomyces cerevisiae* D3. Over 100 carcinogens and noncarcinogens have been tested in this strain as part of an NCI-sponsored contract (154) to evaluate short-term tests. The method does detect a number of carcinogens and is useful, but it is not as sensitive as many of the other short-term tests."

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"6. *Tests for DNA Repair Activity (Unscheduled DNA Synthesis and the Pol Test).*—These tests measure the ability of chemicals to interact with DNA in a way that causes DNA repair to occur. The unscheduled DNA synthesis test (149) measures DNA repair directly in cultured human fibroblasts (cells derived from human skin) after treatment with chemicals. This method is quite sensitive and has been shown to detect a wide range of chemical carcinogens and mutagens. The Pol test is used to detect chemicals that cause particular types of damage in DNA. This type of damage can be repaired by an enzyme present in the bacteria. The Pol test determines the toxicity of the test chemical in mutants that lack the DNA repair enzyme. A positive result is inferred if the chemical under test is more toxic to the bacteria lacking the repair enzyme than it is to the parent strain that contains the enzyme. The Pol test, though useful, is not applicable to detection of a wide range of carcinogens and mutagens. The method has recently been improved (145), and the modified as well as the standard procedures were used in testing saccharin."

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"7. *Drosophila Sex-Linked Recessive Lethal Test.*—The fruit fly, *Drosophila*, can be used to detect a variety of mutagenic and chromosomal breakage events (2). The test used here employs the whole animal and is an *in vivo* test in contrast to most of the other, *in vitro*, short-term tests. *Drosophila* has enzymes that are capable of carrying out many of the same reactions that activate chemical carcinogens in mammalian systems. The most sensitive assay using *Drosophila*, which detects the broadest range of mutagens at the lowest concentrations, is generally considered to be the sex-linked recessive lethal test (2,176), which detects lethal mutagenic changes in the X chromosome. Usually, in this method, male flies are treated with the chemical to be tested (in this case saccharin was added to the nutrient medium), and they are then mated to female flies that have not been treated. Female progeny receive one X chromosome from the female parent and one X chromosome from the male parent; male progeny receive one X from the female parent and one Y from the male parent. Thus, all males carry one X and one Y chromosome, and all females carry two X chromosomes. Even if the one X chromosome

carried by the parental male flies has suffered lethal damage from the chemical treatment (due probably to chromosome breakage caused by the chemical), this damage will not affect the viability of the first generation progeny. A "lethal X" will, in the progeny females, have another healthy X to carry out the needed functions of the X chromosome. A "lethal X" will not be present in any of the male progeny because the one X chromosome in each male progeny is always donated by the female parent, which was not treated with the chemical. The next step in the assay is to mate the first generation daughters to normal untreated males. Now, if one of the X chromosomes carried by the females is the "lethal X", this chromosome will be passed on to some of the male offspring of this second mating. Because males have only one X chromosome, the males receiving the "lethal X" chromosome will die, and in fact such offspring are never hatched. Since so much is known about the distribution of chromosomes among progeny, the experiment can be designed so that a normal mating will result in two phenotypic classes of male offspring. If the class of male offspring that would have received the "lethal X" is missing, then this fact is evidence that the initial chemical treatment, two generations previous, caused lethal chromosome damage in the X chromosome of the treated males."

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"8. *In Vitro Transformation.*—It is by no means clear that the molecular changes that lead to the altered growth potential associated with transformation of cells *in vitro* are the same as the changes that occur during carcinogenesis *in vivo*. However, several lines of evidence strongly suggest that there is a relationship between the processes and that mutagenesis may be the crucial molecular event. *In vitro* transformation tests measure the ability of a chemical to change a cell from a form that cannot cause a tumor in an animal to a form that will result in a tumor if the treated cells are re-injected into the animal.

"Several *in vitro* transformation systems are under development. The hamster embryo (135) and C3H mouse 10T 1/2(143) systems used to test saccharin have both been used to detect a number of carcinogens and mutagens. The National Cancer Institute has recently completed a validation study on the hamster embryo system (135) in which 54 carcinogens and 21 non-carcinogens were tested. The method was quite efficient and was able to detect transforming activity for all but eight of the carcinogens. It did not detect activity for any of the noncarcinogens. The cells used in *in vitro* transformation assays can activate some carcinogens to their active forms. But in order to detect a broad range of carcinogens, these tests have to be coupled to a metabolic activation system. Work is in progress on this alteration in a number of laboratories."

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"9. *Induction of Plasminogen Activator.*—Plasminogen is an enzyme which, when activated, degrades fibrin, a substance involved in the blood clotting process. Many mammalian cell lines, after transformation with viruses or chemical carcinogens, produce a substance that will activate plasminogen. Recently it has been shown that a number of tumor promotors are very potent inducers of plasminogen activator (187). As discussed earlier in this report, some evidence suggests that saccharin has tumor-promoting activity. For this reason, the plasminogen activator assay was included in the saccharin test battery. The plasminogen activator system has thus far been used only for detecting the plant diterpene tumor promoters, and whether it is capable of detecting other types of promoters is not known." (OTA, 1977, pp. 95–106; Exhibit C to Weinstein Statement) (Tables and figures omitted)

Another witness who discussed these tests in some detail was Dr. David Brusick (AIHC) (S. 17).

Another list of short term tests was given in a paper by Purchase *et al.* (1976), introduced by Dr. Matthew Meselson (Harvard Univ.) and by other witnesses. In this paper six tests were described. The Ames test and cell transformation test have been described: the others were:

"*Rabin's test.* The loss of ribosomes from isolated rat liver rough endoplasmic reticulum (RER) following incubation with potent carcinogens in vitro, as first described by Williams and Rabin, has been quantitatively monitored by radio-tracer techniques. An increase (10% or greater) in degranulation of the RER by the test compound, as compared with negative controls was taken to indicate a positive result.

"*Implant test.* A novel technique has been developed based on the histological assessment of the fibrous capsule and surrounding tissues which develop three months after surgical implantation in mice of Millipore filter disks overlain with a gelatinous suspension of the test compound.

The histological appearance of the capsule surrounding each implant was scored on a scale between 1 (low) and 5 (high) based on the appearance of lesions thought to be indicative of neoplasia. The mean scores from control implants containing only DMSO and gelatin were then compared with those from the test implants. Compounds causing a statistically significant increase in the mean score were taken as positive in the test.

"*Sebaceous gland test.* Bock and Mund have demonstrated that the sebaceous glands of mouse skin are sensitive to the topical application of carcinogens. Test chemicals were applied directly to mouse skin and those causing a statistically significant decrease in the ratio of sebaceous glands to hair follicles were taken to be positive.

"*Tetrazolium reduction test.* The test was based on that described by Iversen and Evensen. Samples of mouse skin which had been exposed to the test compound in vivo were incubated in aqueous solutions of tetrazolium red. Statistically significant increases in the in situ biological reduction of the colourless tetrazolium compound to the coloured formazan were measured spectrophotometrically and taken to indicate a positive response for the test compound." (Purchase *et al.* 1976, p. 625; Hearing Exhibit 32)

Several other short term tests were included in a list presented by the NCAB Subcommittee on Environmental Carcinogenesis.

"The intelligent application and interpretation of the *in vitro* tests must also take into account species variations in factors related to the pharmacologic distribution and metabolism of the parent compound as well as possible species differences in macromolecular repair and host defense mechanisms. A number of approaches addressed to the metabolic aspects are now available, including 'host-mediated' mutagenesis assays; the assay of urine and other biologic fluids taken from animals or humans receiving the test compound; the addition of microsomal enzymes and co-factors to the assay system; and the inclusion of specific cells in the assay." (NCAB, 1977, pp. 462–463.)

Another list was given in Dr. Fishbein's report *Potential Industrial Carcinogens and Mutagens:*

"Mutagenicity screening is now apparently both feasible and necessary for chemicals now in, and those which will enter the environment. The mutagenic activity of certain reactive chemicals can be detected in prokaryotic and eukaryotic cells. Short-term microbial tests (in *Salmonella typhimurium, Escherichia coli* and *Bacillus subtilis* in combination with *in vitro* metabolic activation) for mutation-induction include assays for both forward and reverse mutation at specific loci, as well as tests for inhibition of DNA repair.

"The mutagenic activity of some chemicals have also been detected in *Saccharomyces, Neurospora* and *Drosophila.*

"Chemically-induced stable phenotypic changes have been induced in mammalian cell culture systems that include Chinese hamster cells, L5178Y mouse lymphoma cells, human skin fibroblasts and a human lymphoblastoid cell line.

"Unscheduled DNA synthesis (a measure of excision repair) in human fibroblasts has been used as a prescreen for chemical carcinogens and mutagens, both with and without metabolic alteration." (EPA, 1977, p. 4, references omitted, Exhibit to Fishbein statement)

A number of short-term or *in vitro* tests are currently under development and appear promising. These include assays for: the induction of DNA damage and repair; mutagenesis in bacteria, yeast, *Drosophila melanogaster,* or in mammalian somatic cell cultures; and neoplastic transformation of mammalian cells in culture. Other assays that have been employed include the dominant lethal test and studies of chromosomal damage. The latter two tests suffer from the fact that they are frequently non-specific and/or difficult to quantify. Of the various short-term tests, the Ames

Salmonella mutagenesis system has been studied the most extensively. Tests based on other *in vitro* approaches are also being developed.

3. "Validation" of Short-Term Tests

Although a significant number of short term tests is thus available, two of these tests, the Ames test and in vitro cell transformation, have come to be regarded by the scientific community as more "validated" than the others.

A number of witnesses described what they considered to be "validated" short term tests. There was, however, considerable disagreement among these witnesses not only on what tests were "validated" but also on the validation status of several of the tests. From the arguments raised, it was apparent that what constituted a valid test to one scientist did not necessarily constitute a valid test to another. To some witnesses "validation" meant reproducibility, while to others the term meant standardization. To others, the term meant the establishment of a correlation between results in the test and positive results for carcinogenicity. Even the use of these terms was ambiguous. Reproducibility, for example, was used by some witnesses to describe results from other short term tests, while others used the term to indicate concordance with results in long term animal bioassays. Still others referred to reproducibility within the same test or laboratory. Standardization was used to refer to criteria for test protocols in most instances. Often, the same witnesses used the term in several of the contexts described above. It is clear therefore that much of the divergence of opinion about the state of validation of the various tests reflected different uses of the term rather than different interpretations of the scientific data.

The only clear description of how to define a valid study was presented by Dr. Umberto Saffiotti (NCI). Dr. Saffiotti introduced into the record a report of an NCI workshop on *in Vitro Carcinogenesis,* which he edited. In his introduction to the workshop report, Dr. Saffiotti discussed factors which would have to be considered in attempting to validate any short-term tests:

"The research methods needed to provide reliable validation are dependent on several factors: e.g., level of critical quality control of the methods under consideration; extent of their reproducibility; adequacy and accuracy of the in vivo carcinogenesis data against which the in vitro methods are supposed to be validated; number and type of chemicals and chemical groups used in the process of validation.

* * * * *

"I believe that the process of testing the short-term systems for their predictive value in identifying carcinogens should include the following approaches:

(a) Selection of several short-term test systems, including tests for mutagenesis and for neoplastic transformation of cells in culture.

(b) Definition and standardization of laboratory procedures and measurement of their reproducibility, using a small number of test chemicals for each test method.

(c) Selection of a large list of chemicals as reference compounds, including direct carcinogens, procarcinogens and noncarcinogens. About 100 compounds have been used by the NCI Carcinogenesis Program in the evaluation of mutagenesis test systems (35, 44, 45); the Ames test has been evaluated using an additional 200 chemicals in various laboratories (35). In the hamster embryo cell transformation system, a list of about 75 chemicals has been tested so far (42). The list of reference chemicals needs to be evaluated for their reliability in terms of in vivo carcinogenesis data. It is important to include a sufficiently large number of noncarcinogenic reference chemicals. These lists should be periodically extended and revised to include a representative range of chemical classes. I believe that in a second phase, each biological test system should be screened using nearly all the available chemicals for which extensive reliable data exist on carcinogenesis bioassays in animals (perhaps 500 to 600 compounds).

(d) Definition of biological metabolic activation systems and of the metabolic requirements for each of the chemicals of the reference list.

(e) Systematic screening of the selected chemicals in the selected bioassay systems, including tests for reproducibility and by a double blind procedure.

(f) Comparison of the response of different test systems, with particular consideration for the susceptibility of different cell systems with regards to host and tissue of origin.

(g) Concurrently, much new imaginative research is needed in the following areas: development and definition of new cell transformation systems, with emphasis on epithelial cells and on human cells; metabolic activation mechanisms; relation of mutagenic to carcinogenic events in the same target cells; biochemical mechanisms involved in transformation; markers of the transformed state; and definition of culture conditions.

"The NCI Carcinogenesis Program has undertaken an extensive effort towards the development and validation of short-term methods for carcinogenesis screening, and towards their definition and interpretation along these lines." (Saffiotti and Authrup, Eds., 1978, pp. 3, 9–10; Exhibit to Saffiotti Statement)

The IARC preamble discussed several difficulties which must be considered in any validation process:

"The results of validation studies could be strongly influenced by such selection of chemicals and by the proportion of carcinogens in the series of chemicals tested; this should be kept in mind when evaluating the predictivity of a particular test. The usefulness of any test is reflected by its ability to classify carcinogens and noncarcinogens, using the animal data as a standard; however, animal tests may not always provide a perfect standard. The attainable level of correlation between short-term tests and animal bioassays is still under investigation.

"Since many chemicals require metabolism to an active form, test systems that do not take this into account may fail to detect certain potential carcinogens. The metabolic activation systems used in short-term tests (for example, the cell-free systems used in bacterial tests) are meant to simulate the intact human." (IARC, 1978, Vol. 17, p. 26)

With these considerations in mind, IARC listed four tests as "validated": the Ames test, the X-linked recessive lethal test in *Drosophila melanogaster,* unscheduled DNA synthesis, and *in vitro* transformation (*id.*) Several other witnesses listed the Ames test as validated (e.g., Meselson, Tr. 1476; McCann, Tr. 1551–1552). Dr. Leon Golberg (CIIT) considered the dominant lethal test to be "validated" (Tr. 6530). Dr. Umberto Saffiotti (NCI) discussed several short-term tests using mammalian cells in culture in which he felt confident:

"I shall limit the present discussion to the use of tests for the neoplastic transformation of mammalian cells in culture by chemical substances. Methods for such tests have been developed in several laboratories since the first report by Berwald and Sachs (1965). Some of these methods are currently extensively used in several laboratories with good reproducibility and have been found to respond to a large variety of chemical carcinogens. Two types of test systems have been so far most widely studied. They are: a) the golden hamster embryo cell system, which uses primary and/or secondary cultures of normal embryo cells; and b) the mouse embryo fibroblast cell line system, which uses established homogeneous cell lines, particularly the C_3H 10T ½ clone 8 cell line.

"Other systems, which utilize other cell types, including epithelial cell systems, are currently being developed and defined.

"A number of criteria have been developed for the recognition of induced neoplastic transformation, including colony morphology, growth in special culture media, and the production of neoplastic growth following inoculation into immunocompatible or immunosuppressed animals. Comprehensive documentation on these methods is included in two recent review books (Montesano, Bartsch and Tomatis, Eds., 1976; Saffiotti and Authrup, Eds., 1978). These methods require competent professional skills and judgment for their performance and evaluation." (Saffiotti, S. 35–37)

During the hearing, a number of confounding factors were introduced to question the "validity" of short term tests, especially the Ames test. Dr. Meselson (Harvard Univ,) discussed one of these points, use of substances such

as phenobarbital or PCB's to activate the enzymes in the liver extracts used in the Ames test. Dr. Meselson argued that these substances may still be present after activation and may influence the results. However he did not feel this would invalidate the tests:

"No, it just contributes to the background that you find, and there is always going to be a background due partly to the natural reversion of these histidine mutations. And it is true that when you put on the liver paste you raise the background slightly. Something in it is raising the background. What exactly that is there are lots of—after all, those livers are coming from mice who are real animals or rats who are real animals and real animals die of cancer. Human population, 25 percent of us will get cancer, 25 percent as measured from birth; 17 or so percent of Americans die of cancer. It is not any different with other mammals. They all are susceptible to cancer. So it is not surprising that there is something in them. In fact, the reason I got interested in this potency correlation was the rather naive biochemical question, could you grind up animals so to speak, and get an extract and then fractionate this in the usual ways that biochemists fractionate complex mixtures on chromatographic columns, and then devise some assay to see which are the active fractions and then fractionate those further, until finally, you isolate a single pure compound and identify it chemically to find out what are the carcinogens really in our bodies that are actually causing the prevalent rate of cancer. A kind of brute force, head-on and naive attack on the cancer problem.

"Now, to answer the question of whether you could take that approach, I need to know is there an assay which is sensitive enough. So I had to begin thinking about how do you measure sensitivity. Not sensitivity to mutation but sensitivity in terms of cancer. And that led me to ask is there a correlation in fact between the sensitivity in the Ames test to mutation on the one hand, and the potency of a compound as a carcinogen. So, yes, I think there are undoubtedly some carcinogenic molecules in that liver extract. There are certainly some mutagenic ones. They come from animals who are dying of cancer; all animals are dying of cancer at some probability. Or getting cancer." (Meselson, Tr. 1528–1529)

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"Well, the results would be valid in any case because you always do some tests where you do not have the compound, and you get a background number of colonies. And the test is significantly positive only if the chemical you add gives something which is for sure significantly above that steady background. Now, all that the liver paste does in the respect you are talking about here is to contribute a little to the background. It also greatly enhances the signal if it is a compound that needs activation, but it does contribute a little to the background. So in that sense, the sense you are talking about, it slightly limits the sensitivity of the Ames test; slightly limits it by contributing a little bit more to the background, thus increasing the likelihood that you might not pick up something which is actually positive." (Meselson Tr. 1530)

Dr. McCann discussed another problem, the fact that DNA repair mechanisms in the bacteria tester strains are not the same as those in humans or even in the parent bacteria from which the tester bacteria are derived:

"There have been two alterations inserted into the bacteria, each dealing with different kinds of repair activities in the cell. And in general, one could divide the repair activities into two groups: One sometimes called the accurate repair system or the UV repair system, and these are enzymes that recognize lesions in DNA and clip them out and sew the DNA back up, in effect.

"And one of the primary things that characterizes them is that they do not make mistakes. They do a very accurate job of it, and that is why this system is often called the accurate repair system.

"Well, one of the modifications put into the bacteria was to introduce a mutation into one of the genes that govern one of the enzymes in that system so that that capability in these bacteria is much reduced from what it is in the wild type.

"Now, I think the crucial question there, and it is a very legitimate one, is: do you create mutagens by doing that? Well, in fact, all of the evidence indicates that we do not, because what happens is that that increases the sensitivity of the test in that a weakly mutagenic substance becomes a more potent mutagen. It is easier to detect, and for a screening test, that is very important.

"There is not a single example of a chemical that is a mutagen in the repair-defective strain that is not a mutagen also in the wild type. It becomes a much stronger mutagen, and it makes the test much more effective for picking up activities. It does not create anything.

"The second repair system is similar to the first, I think much less understood, but it might be characterized by the fact that it performs a similar function in that it recognizes lesions and repairs DNA, but it does not do it as accurately. It makes mistakes, and that is sometimes referred to as the error-prone repair system.

"Now, in two of the bacterial strains we use, and we use generally a total of about four—in two of these strains, there has been what was mentioned this morning, a plasmid, which is basically just an extra piece of DNA inserted into the bacteria that has the apparent effect of enhancing the error-proneness of that repair system.

"So that when lesions are introduced into the DNA, in the process of their repair, that process has a much better chance of making a mistake, and a mistake is translated into a mutation. So again, the effect is not a qualitative change in that we do not create mutagens, but it greatly increases the sensitivity of the test so that chemicals that in the strains without the plasmid are very, very weak mutagens become very, very strong." (McCann, 1558–1560)

Dr. McCann continued to discuss another factor, the removal of the outer cell surface of the bacteria:

"The lipopolysaccharides coat the surface of bacteria normally, and they are sort of sticky substances that function to protect the bacteria. The reasons for that is also to increase the sensitivity, and large molecules that ordinarily apparently tend to get stuck in that outer sticky coating can then come in." (McCann, Tr. 1560)

Dr. McCann expressed the opinion that these differences did not in any way detract from the results of these tests:

"It is acting differently in the manner of degree, in a quantitative sense, but not in a qualitative sense, which I think is a very important distinction when one is trying to grapple with, first of all, the fact that here we are using bacteria and trying to get information about people. I mean, I think that is a difficult thing to grapple with in the first place, and then realizing that we have put modifications into the bacteria makes it even more difficult to grapple with.

"But I do not find any theoretical objection to this whatsoever, and on top of it, one has to superimpose the enormous amount of evidence that it works, which also is an important element." (McCann, Tr. 1560–1561)

4. How Well Do Short-Term Tests Predict Carcinogenesis?

The use of short-term tests for mutagenicity to predict carcinogenic potential is predicated upon the existence of a correlation between carcinogenic and mutagenic activity of chemicals. Several witnesses presented evidence for such a correlation. In particular, Dr. David Brusick (AIHC) presented detailed documented evidence to support the assumed relationship:

"A Mechanistic Link Between Mutation and the Induction of Neoplasia

"17. If STT are capable of identifying chemicals with carcinogenic potential for mammals, there must be a relationship between specific types of genetic alterations and the production of malignant cells. Logically, this relationship would appear evident in the nature of neoplastic diseases.

"18. The following points all contribute to the logic trail leading to the proposed link between mutation and cancer (31).

(a) Tumors appear to result from the process of cell transformation following cell proliferation. Every cell which undergoes transformation to a malignant state will not produce a tumor because of immune surveillance and other *in vivo* control phenomena. Tumors appear to be clonal in origin (2), which is evidence for a single cell origin.

(b) Transformed malignant cells have phenotypic properties which are different from their nontransformed precursor cells (3). This is evidence that a genotypic change has produced the new phenotype.

(c) Transformed cells transmit their phenotypic properties to all progeny cells.

This is evidence that the control of malignancy is associated with the hereditary components of the altered cell. The Central Dogma Hypothesis of Crick and Watson would ascribe the change to the DNA molecule.

(d) Transformed cells will grow into a tumor if transplanted into a healthy syngeneic host animal (4). This is evidence that the tumorigenic properties are directly associated with the malignant cells.

"19. Chemicals which have been shown to produce mutagenic changes in DNA and especially those demonstrated to produce such changes in mammalian cells would, therefore, be potential carcinogens. Other pieces of indirect evidence support the assumption that DNA lesions provide the basis for malignant transformation. For example, many chemicals produce cancer through the formation of carcinogenic intermediates following metabolic activation (5). These carcinogens, called procarcinogens, are inactive until enzymatically converted to the biologically active form. Generally, the mixed function oxidase (MFO) enzyme system associated with the rough endoplasmic recticulum of cells is involved in the biotransformation of chemicals to their active form (6). It has been demonstrated that the mutagenic properties of procarcinogens are also associated with the carcinogenic intermediate (7,8). For several procarcinogens the active carcinogen has been established and it is the same molecule which is genetically active (9). A concordance between these two activities would be mandatory only if mutation is a prerequisite step leading to malignancy.

"21. Essentially all chemicals known to directly initiate cancer in mammals are active mutagens or produce mutagenic metabolites. Numerous comparative studies support this relationship (10,11,12,13,14,15) and if the mechanism postulated in figure 1 approximates the events which actually occur in malignant transformation, then to conclude that all chemical mutagens are potential carcinogens is not an overstatement of the data. However, it must be emphasized that a potential carcinogen cannot be equated with an established mammalian carcinogen." (Brusick, S. 6–9)

Dr. Ronald Hart (Ohio State Univ.) also presented detailed testimony on the correlation between carcinogenesis and mutagenesis:

"Until recently, support for the somatic mutation theory of cancer had not been enthusiastic; since many potent carcinogens were found to be non-mutagenic in early test systems.[3] Indeed, it is still generally agreed today that not all carcinogens are mutagens. For many of those carcinogens which do appear to be mutagenic (conservatively at least 70%), metabolic activation has provided an explanation for the earlier observation that many potent carcinogens were not mutagenic. The Millers found that most all chemical carcinogens were either electrophiles *per se* or could be metabolically activated to electrophilic species.[4,5] When, subsequently, activating systems* were added to the mutagen test systems, virtually all chemical carcinogens were mutagenic.[6] Investigators of recent years have shown a strong correlation between the carcinogenicity and mutagenicity of a variety of chemical and physical agents (presumably reflecting, in many cases, the ability of an agent to cause DNA damage thereby altering the normal base sequence of DNA).[6] Data from a number of mutagen test systems which employ either microsomal homogenates (the cellular subunit which contains enzymes capable of modifying certain chemical agents to a form in which they will cause cancer) or feeder cells (cells containing the aforementioned enzymes) indicate that there is for selected chemicals a 90% correlation between carcinogenicity and mutagenicity.[6–9] This correlation is strong support for the somatic (nongerm cells*) mutation theory of cancer originally proposed by Boveri.[10] Acceptance of the somatic mutation theory proposed makes it reasonable to consider DNA as a critical cellular target for many chemical carcinogens.

"14. DNA was initially assumed to be the target macromolecule for chemical and physical carcinogens for the same reasons it was presumed to be for the lethal and mutagenic effects of X-rays and ultraviolet (254 nm) light: (a) it is the largest macromolecule in the cell and thus has the greatest probability of interacting with any electrophilic agent; (b) unlike other macromolecules it appears in a unique copy and thus damage to it would be expected to have greater consequence for cellular behavior than damage to, for example, 1 out of 50 identical RNA molecules or 1 out of 500 to 1000 identical proteins; (c) it serves as the template for synthesis of most other cellular macromolecules and thus damage to it would be expected to propagate throughout the cell; (d) unlike RNA, lipids, and proteins, there is no turnover of DNA and thus damage to DNA may be expected to be comparatively stable if not repaired; (e) since most cancers appear to be clonogenic, it is a reasonable assumption that the alteration responsible for the transformed state must be inheritable between cell generations, thus implicating a genetic change.[11]

"15. In addition to the intuitive evidence presented above, several recent studies have provided indirect and direct evidence that DNA damage plays a causative role in carcinogenesis. It now appears that virtually all major classes of chemical carcinogens bind to DNA [3,12,13] and, further, that either the extent of binding (to be outlined below) or the absence of subsequent removal of such DNA-chemical bonds (to be covered in Section 2) correlates well with the carcinogenic potential of these agents. The types and extent of DNA-chemical interactions vary as a function of the agent, cell type, species, and physiological environment.[11] Evidence that physical and many chemical carcinogens interact with cellular DNA, and produce distortions (via either dimerization,[14] substitution at various nucleophilic sites on the heterocyclic bases,[12,15] phosphotriesters [16,17] and/or inter- and intra-strand crosslinks [18]) in that macromolecule resulting in carcinogenesis and/or mutagenesis is presented below. . . .

* * * * *

"16. Hence, in summary, it is clear that most, but not all, chemical and physical carcinogens damage cellular DNA. Further, it is clear that for many chemical carcinogens, metabolic activation is required for them to effect their interaction with DNA and exhibit their mutagenic and carcinogenic potentials. The mutagenic and carcinogenic potential of many chemical carcinogens appears to be related to both the extent of their binding of DNA and the chemical nature of the bond they form with DNA. It is thus a reasonable assumption that differences in the metabolic activation potential of liver homogenates and cell feeder systems would be reflected in the extent of binding of the active chemical species to the DNA." (Hart, S. 7–9, 14)

Dr. Hart made the following conclusions about the associations between carcinogenicity and mutagenicity:

"35. The presently available evidence suggests that:

(a) DNA is the primary target for most but not all physical and chemical carcinogens;

(b) For many chemical carcinogens metabolic activation is required to produce the carcinogenic form of the agent;

(c) DNA repair (of at least the excision form) appears to modulate the cytotoxic, mutagenic and carcinogenic potential of physically or chemically induced DNA damage;

(d) Correctly repaired DNA damage is assumed to have no deleterious biological effect;

(e) Unrepaired DNA damage, entering DNA replication, is believed to produce mutations by either misreplication or misrepair;

(f) For many, but not all carcinogens, mutagenesis appears to correlate well with carcinogenesis. (Hart, S. 27–28)

Dr. Joyce McCann also presented detailed documented evidence on the correlation between mutagenesis, specifically as measured by the Ames assay, and carcinogenesis. As discussed earlier, she presented these data as scientific evidence to support OSHA's proposed use of short-term tests:

"1. When short-term tests are evaluated for their ability to detect known human carcinogens the same way animal carcinogenicity tests are evaluated, they fare equally well with the animal tests with the one exception of diethylstilbestrol (DES).

"Short-term tests detect all known human carcinogens, with virtually the same exceptions as for animal tests. Neither short-term tests nor animal carcinogenicity tests have yet convincingly detected the suspected human carcinogens arsenic or benzene. All the organic chemical human carcinogens (except benzene and DES) are detected in the *Salmonella* (Ames) test (Table 1), asbestos causes chromosome aberrations (2), the metal carcinogens are detected in *in vitro* tranformation tests (3). Given that there are about 25 known or suspected human carcinogens, this correspondence between animal carcinogenicity tests and short-term tests is striking.

"Although the short-term tests currently available efficiently detect carcinogens that

interact with DNA, they may not detect carcinogens that act through non-mutagenic mechanisms. Though there is much evidence to indicate that the great majority of carcinogens are mutagens, it is reasonable to suppose that there will be carcinogens which are not mutagens. DES, a human carcinogen, is an example which most likely acts through a hormonal, non-mutagenic mechanism. The carcinogenic activity of DES can be detected in mammalian carcinogenicity tests, but not in short-term tests currently available. This points out an important limitation of short-term tests even when batteries of tests are used, and emphasizes the continuing need for animal carcinogenicity tests.

"2. Retrospective validation studies comparing results in short-term tests with those from animal carcinogenicity tests indicate a very high correlation between the two general methods of detection and suggest that both methods will more often fail to detect carcinogens than they will falsely detect them.

"The major limitation of short-term tests is that they detect fewer chemicals as positive than the animal carcinogenicity tests. This problem can be minimized by using an appropriate battery of tests, but even if batteries of tests are used this limitation will most likely still be the major source of error from short-term tests. Comparisons of results in short-term tests and animal carcinogenicity tests have indicated that, provided both the positive short-term test data and the animal carcinogenicity data are adequate, there is no clear example of a true "false positive" of which I am aware. For results in the *Salmonella* test, Bruce Ames and I have discussed this in detail (4, 5, 6) (see Appendix). In general, however, the theoretical possibility of true false positives from short-term tests is very real. For example, activation pathways or repair mechanisms that are different from those found in humans are certainly a possibility. At this time the non-mammalian short-term tests are the most sensitive and versatile of the currently available methods. Nevertheless, because of their distance from mammals, and the theoretical reasons for false positives, I believe that at least one short-term test using eukaryotic, or mammalian cells should be positive in the battery of short-term tests required to elevate a chemical from Category II to Category I status.

"3. There are an increasing number of examples where short-term tests have accurately predicted the carcinogenic potential of chemicals.

"The evidence is now quite strong that almost all human and animal carcinogens are mutagens. It is a somewhat different question, however whether chemicals that are turned up by short-term tests will be found to be carcinogens (i.e., are mutagens carcinogens?). Ultimately, in evaluating the usefulness of short-term tests as predictors of carcinogenicity, this is the more relevant of the two questions. Although such data takes much longer to generate because we must wait for the cancer tests, there is a growing list of carcinogens that were accurately predicted by short-term tests. In fact, there is not so far a single example of a wrong prediction. It is important that we keep a close watch on this growing list, so we may identify any false predictions that turn up. So far, short-term tests are proving to be excellent predictors of carcinogenicity, and I believe the evidence to date is ample to justify OSHA's proposed use of short-term tests.

"Some examples are: (1) *Ethylene dichloride*, recently reported carcinogenic in NCI animal carcinogenicity tests, has been known to be a potent mutagen in *Drosophila* for many years (7). (2) *Dibromochloropropane* (DBCP), recently found to cause sterility in humans, was found to cause sterility in animals a number of years ago and evidence of carcinogenicity in animals and mutagenicity in short-term tests also preceded the human evidence (discussed in 8). (3) *Tris*, the flame retardant, was first reported mutagenic in the *Salmonella* test (9), subsequently found positive in many other short-term tests before the observation that it caused cancer in animals. Other examples are dye components in oxidative hair dyes (10), ethylene dibromide, nitroquinoline-N-oxide, and the Japanese food additive AF–2 (see (6) for references)." (McCann, S. 5–9)

Dr. David Rall (Director, NIEHS) also commented on the correlation between mutagenicity and carcinogenicity:

"I think the evidence from the Ames-type test and the other tests is very strong that there is a high degree of correlation between carcinogenicity of non-hormonal organic chemicals and the—particularly the Ames and the other mutagenesis or rapid in vitro tests." (Rall, Tr. 367–368)

As did Dr. Arthur Upton (Director, NCI):

"The short-term test may help us in determining that the substance in question is, in fact, genotoxic, is capable of attacking the genes of the cell. We know there is a very high correlation between genotoxicity or mutagenicity and carcinogenicity. The correlation is not perfect and so we cannot rely on genotoxicity as a measure of carcinogenicity." (Upton, Tr. 290)

Other witnesses who agreed that a strong correlation exists between mutagenicity results from short-term tests and carcinogenicity results from long-term animal bioassays included Dr. Roy Albert (EPA), Tr. 2381; Dr. David Hoel (NIEHS), S. 8–9; Dr. Peter Goldman (Harvard Univ.), S. 15; Dr. Bernard Goldstein (New York University), S. 2–3. A number of studies have been conducted which set out to establish what correlation did exist for groups of chemicals between carcinogenic results and mutagenic results in short-term bioassays. The most comprehensive of these "validation" studies was carried out by Dr. Bruce Ames. Dr. Matthew Meselson described this investigation.

"Dr. Bruce Ames of the University of California at Berkeley and his colleagues have reported the results of testing nearly 300 chemicals for mutagenicity according to the methods worked out in their laboratory. The results were then compared with those of published long-term carcinogenicity tests on laboratory rodents. Most (84%) of the chemical carcinogens were found to be mutagenic (157/175), while most (88%) noncarcinogens were not found to be mutagenic (95/108) (McCann et al., 1975)." (Meselson, S. 6)

Dr. McCann, who collaborated with Dr. Ames in this study, commented that the purpose of the study was to find out if the results of the Ames test were "meaningful" to people in predicting the potential carcinogenicity of a substance. Dr. McCann continued:

"And so for that reason, we had to undertake some kind of validation attempt to see if we, in fact, were getting information which was relevant to what we were interested in.

"There are so few chemicals that are known to cause cancer in people. There may be about 25, but that is not a long enough list. We did look at those, and the test detects virtually all of the organic chemical carcinogens, and it is interesting that it only misses the chemical carcinogens that appear to be also missed in the animal cancer tests, which I think is significant.

"But what was needed was clearly a much bigger list, and also what was needed were a number of chemicals that looked like they were not going to be carcinogens in people. And so for that reason, we had to go to animal cancer data, because there are large numbers of chemicals that have been tested in animals, and there are large numbers that have been positive and large numbers that have been negative.

"So we made a comparison of the results in our test with the results in animal cancer tests. Now, when one does that kind of exercise, I think one has to realize at the outset that since both test systems are imperfect, there are going to be some mistakes generated due to the imperfections from both.

"Some of the mistakes will be due to animal cancer test problems. Some of the other mistakes will be due to the Salmonella method.

"What in fact happened is that we did have some noncorrelations. We had some false negatives in Salmonella, chemicals that were carcinogens in the animals, and we had some so-called false positives, chemicals that were positive in Salmonella but negative in the animal cancer test.

"So what we did in those cases is look at the data from both systems, and what we found is that the animal cancer test data for the chemicals that showed some mutagenic activity in our tests but were negative in the

animal cancer tests was in general very limited. The tests, most of them were clearly defective in that they would have very few animals or cover a very short duration.

"And in fact, false negatives in animal cancer tests is the biggest problem of animal cancer tests. This is because you can only do them with a limited number of animals.

"There are a number of examples of animal carcinogens that have been negative in one or two animal cancer tests and then positive in another. One of the most interesting examples is something called furyl furamide, or AF–2, that was used as a food preservative in Japan for about eight years. And they tested it in animals before putting it in food, twice, in two animal cancer tests that were not horrible tests. They were fairly decent tests, and it was negative.

"After the eight years, Dr. Sugimura working in Japan, using a method very similar to ours, a bacterial test method, was starting to look at food, and he put a slice of fish sausage that happened to contain this preservative on a petri dish and found a large number of revertant colonies coming up around the fish sausage, which indicated the fish sausage was mutagenic.

"He then started purifying the chemical from the fish sausage, thinking he was going to find a natural part of fish sausage mutagenic, and it turns out it was the food additive.

"That chemical was then put back into cancer tests, and they designed the test so that it was more complete. They used more animals. They did generally a more complete test, and it turned out positive. And it has been banned now. In fact, they withdrew all the food that contained it.

"But there are a number of examples of that, and I think in general, animal cancer tests are proving themselves to be—they are very good, in one sense. They are weakest, I think, in the area of detecting weaker carcinogens and in the area of false negatives.

"So for the chemicals that registered positive in our tests that were negative in the animal cancer tests, my personal feeling is that I do not believe there is a good example of a true false positive among those.

"Now, I do not mean by that to rule out the possibility of false positives because I think that is a very important point, that there may be some, but I think we need to be willing to make a few mistakes. I think the most important thing is that all the evidence we have now from Salmonella, from the other short-term tests, is that the mistakes we make are going to be proportionately very, very few." (McCann, Tr. 1583–1586)

As previously mentioned, Dr. Meselson introduced a paper by Purchase *et al.* (1976) which evaluated six short-term tests for their ability to detect known carcinogens. These authors tested 58 carcinogens and 62 non-carcinogens in each of six short-term tests, conducted under standardized conditions. The highest correlations between the test results and previously reported carcinogenicity were obtained in the Ames test (which gave "accurate predictions" for 91 percent of the carcinogens and 93 percent of the non-carcinogens) and *in vitro* cell transformation (91 percent and 97 percent respectively). Rabin's test, subcutaneous implants, sebaceous gland suppression and tetrazolium reduction gave less "predictive" results (ranging from 37 to 95 percent).

Dr. David Brusick (AIHC) also introduced a table in which results of animal bioassays were correlated with results from short-term tests. Dr. Brusick summarized several "validation" studies as shown in Table 1 below. This table shows a range of "correct designations" from 85–95%. Dr. Brusick commented on this table:

"The results of the studies summarized in Table 2 indicate that some chemicals classified as carcinogens do not exhibit genetic activity in STT. Since it is unlikely that all of these chemicals were incorrectly classified by rodent bioassay studies, the origin of cancer in mammals may not be a single type of mechanism. Certain chemicals appear to be mammalian carcinogens but are not clearly capable of producing genetic alterations in STT." (Brusick, S. 10)

Table I.—*A Summary of Some Validation Studies on Selected Short-Term Tests (From Brusick, Table 2, References Omitted)*

Test	Approximate number of chemicals evaluated in the reported studies	Approximate percentage of correct designations	Estimate of the unreported compounds evaluated in similar tests[a]
Ames test	[b]420	90	4,000–6,000
Transformation Test	87	90	255–300
Mouse Lymphoma Test	[c]32	95	500
Sister Chromatid Exchange	[c]14	80	50
Drosophila (SLRL)	[d]100	90	1,000–2,500
Unscheduled DNA Synthesis	[c]16	87	100–200
In Vitro Cytogenetic Analysis	134	[e]85–95	1,000–2,500

[a] This estimate is based on estimates of in-house testing by private firms including contract laboratories. It gives an estimation of the experience factor associated with the tests and an indication of their use in chemical testing. These estimates represent results on unique compounds.

[b] This data represents tests on compounds common to both studies.

[c] Number of reported chemicals insufficient for accurate determination of reliability.

[d] Polycyclic hydrocarbons are generally negative in *Drosophila*.

[e] The value depends on criteria for (+) and (−) designations.

Several witnesses questioned the reliability of the reported correlation between long term animal bioassays and results in the Ames assay. For example, the CIIT workshop report asserted that the high correlation was misleading due to "judicious selection of the chemicals used" (exhibit to Golberg testimony, pp. iv-v). However, this comment would not be applicable to the study by Purchase *et al.* (1976), who used a wide range of chemicals. Dr. Samuel Epstein (Univ. of Illinois) referred to a study by Legator in which 494 chemicals in 45 structural classes were tested, and in which a correlation between carcinogenicity and mutagenicity was found only in certain classes. However, Dr. Ames and his colleagues have responded to these criticisms by pointing out that at least some of the purported discrepancies are due to the insensitivity of animal bioassays with resulting "false negative" results for carcinogenicity:

"Maugh also quotes Lijinsky as saying the *Salmonella* (Ames) test is not a useful qualitative predictor of carcinogenicity on the basis that it has only a 55 percent correlation for a group of polycyclic hydrocarbons that he tested for both mutagenicity and carcinogenicity (11). However, the Ames test has been extensively validated in three independent studies (12, 13), all of which agree that approximately 90 percent of the carcinogens from a wide variety of classes were mutagens in the test. Furthermore, Lijinsky's study does show that the *Salmonella* mutagenicity assay is an excellent test for the detection of carcinogenic polycyclic hydrocarbons: 88 percent of the carcinogenic hydrocarbons analyzed (14 out of 16) were mutagenic in *Salmonella*. This agrees with a large study on polycyclics by Coombs et al. (14), in which 38 out of 38 carcinogenic polycyclics were mutagenic in the test.

"Lijinsky obtained the "55 percent correlation" estimate by combining his results on the 16 carcinogens with the 8 "noncarcinogens," of which 8 out of 8 were mutagens. Unfortunately, Lijinsky accepts the results of limited or inadequate cancer tests as definitive evidence that a chemical is a "noncarcinogen." But the word "noncarcinogen" has meaning only in the context of an analysis of the power of the

test. We have discussed elsewhere (15) the problems with using Lijinsky's insensitive cancer tests for determining whether or not a chemical is a "noncarcinogen." His analysis of carcinogenicity was based entirely on skin painting studies, which are considerably less sensitive than the standard NCI feeding studies and do not meet NCI criteria for an adequate test. It remains problematical whether his skin painting studies would have detected very many of the known human carcinogens at the doses used, although the *Salmonella* test detects almost all of these (13)." (Hooper *et al.*, 1979, pp. 602–603)

Purchase *et al.* (1976) raised another procedural question:

"The main appeal of short term tests is that they seem to offer a method of rapidly searching a group of compounds for potential carcinogens in order that priorities may be set for conventional long term studies. However, the drawback to using even relatively reliable tests for such purposes is that the proportion of positives produced which would be expected to be false may become very large. It is not possible from the present study to accurately estimate this proportion, but the model shown in Table 4 illustrates the nature of the problem which may be encountered. For example, in the model the effect of using a test which was known to be 90% accurate to screen an arbitrarily selected sample of 1,000 chemicals containing 10 carcinogens (1%) would be to generate 108 positive results of which only nine would be carcinogens. There would, therefore, be only an 8% chance that a compound which was positive in the test would be an animal carcinogen. Conversely, in the present example, the probability that a compound which gave a negative result in the test would be a non-carcinogen would be greater than 99%. (Purchase *et al.*, 1976, pp. 626–627)

This point was referred to by Dr. Francis Roe (AIHC; S. 51–52). However, in making his comment, Dr. Roe failed to address the specific proposal under consideration. OSHA does not intend to regulate compounds on the basis of one short-term test alone. In order to guard against the likelihood of false positive results of the kind referred to by Purchase *et al.*, OSHA intends to rely on results from more than one short-term test, combined with the results from at least one long-term animal bioassay, as the basis for instituting regulatory action. The probability of obtaining false positive results is greatly reduced by requiring a second corroborative test. The probability of obtaining false positive results in one animal bioassay *and* in more than one short-term test is vanishingly small.

There were a number of other witnesses who did not agree that there was a correlation between mutagenicity and carcinogenicity which could be used for predictive purposes. These commentors include: Dr. Rulon Rawson (Univ. of Texas), S. 4–5; Dr. Francis Roe (AIHC), S. 53–54; Dr. Paul Kotin (Johns-Manville), S. 22; Crompton and Knowles Inc., S. 3; and Dr. William Lijinsky (NCI–FCRC), S. 25.

However, these witnesses offered no specific data that would offset the reliability of the correlations reported by Purchase *et al.* (1976), Sugimura *et al.* (1976), McCann *et al.* (1975), and the other authors cited by Dr. Brusick. Thus, although OSHA recognizes that there is some divergence of opinion, OSHA concludes that there is in fact a better than 90 percent correlation between the results of certain short-term tests and animal bioassays for carcinogenicity. Thus, with due regard for the possibility of obtaining occasional false positive results in single tests, OSHA believes that the requirement of more than one of the short-term tests under consideration creates a very high predictive value.

5. What Degree of Confidence Do Short-Term Tests Add to the Results of Animal Bioassays in the Evaluation of Carcinogenic Risks for Humans?

A number of witnesses commented that short-term tests added a strong sense of confidence to the results of animal bioassays. Dr. David Rall (Director, NIEHS) expressed the point as follows:

"There is no question that positive results in short-term tests (such as the Ames test, induction of unscheduled DNA repair, or malignant cell transformation *in vitro*) add to the confidence that one would have in a single positive animal test. This is not to say that these short-term tests are *equivalent* to lifetime bioassays in rodents: it merely reflects the fact that most carcinogens give positive results in short-term tests. Hence, if there is any reluctance to accept the result of a single animal bioassay, positive results in short-term tests would add sufficient evidence to overcome this reluctance. Certainly, it seems reasonable to use them in this way rather than to demand a second lifetime test in a rodent, which would be lengthy and expensive." (Rall, S. 14)

Dr. Roy Albert (EPA) expressed a similar opinion when he agreed that a short-term test would increase his confidence in the significance of a marginally positive result from an animal bioassay (Tr. 2380). However, Dr. Albert stated a slightly different opinion about negative results in short term tests:

"The correlation is generally pretty good between positive mutagenicity and positive carcinogenicity, so that negative results [in mutagenicity tests] tend to diminish the strength of the evidence to some extent, but I do not think to the extent that positive results actually strengthen the evidence. That is almost an unfair way the game is played." (Albert, Tr. 2381)

Dr. Lawrence Fishbein (NCTR) felt that mutagenicity test results added to his confidence in results from animal bioassays, especially when used in conjunction with available structural similarities. Dr. Fishbein commented that these data should be sufficient to "boost a compound from Category II to Category I" (Tr. 1824).

Other witnesses commented that it was difficult to address this question because they felt that *one* animal bioassay alone was sufficient to provide evidence that a substance posed a potential carcinogenic risk (Bates, Tr. 666; Kimbrough, Tr. 1794–1795).

However, these witnesses agreed with Drs. Rall, Albert, and Fishbein, that positive results in short-term tests add to the weight of evidence for potential carcinogenicity (Bates, Tr. 645; Kimbrough, Tr. 1794–1795). Thus, although few witnesses addressed this specific issue, there was substantial evidence in the record from eminent scientists to support the conclusion that positive results in one or more short-term tests would increase the degree of confidence that should be placed in the results of one otherwise uncorroborated long-term carcinogenicity bioassay.

6. Can a battery of short-term tests be developed which would provide reasonable predictions of carcinogenic activity, and if so, what criteria should be met by such a battery?

Many witnesses recommended to OSHA that the use of a battery of short-term tests is the best approach to using and evaluating the results of these tests. The major limitation of short-term tests is that no one test is likely to detect all animal or human carcinogens. Thus, if only one test is used, a substantial number of false negative results is expected. This problem can be minimized by using an appropriate *battery* of tests. Dr. Joyce McCann (Univ. of California) presented a detailed rationale for the use of a battery of tests:

"1. Some short-term tests detect certain classes of carcinogens that other short-term tests do not. The use of complementary short-term tests in test batteries can help to minimize false negatives.

"2. By requiring that positive results in a short-term test be verified by a positive result in other short-term tests, batteries will help to minimize false positives. Although many of the individual short-term tests are proving to be highly predictive, and there are as yet no clear cut examples of false positives, the theoretical possibility of error remains. Since short-term tests can be done with relative ease (compared to doing an animal carcinogenicity test) it seems prudent to require that before regulatory action is taken, that any positive result in a short-term test be

verified by a positive result in other short-term tests.

"3. One of the strengths of short-term tests is their ability to rapidly supply information from a variety of test organisms and metabolic activation conditions. Such information cannot be obtained from animal cancer tests, but can be obtained from batteries of short-term tests, with relatively little extra expenditure of time and energy. To do less would be to under-utilize this valuable source of toxicological information. (McCann, S. 10–11)

Dr. McCann elaborated on what she meant by a battery of short-term tests in her oral testimony:

"No single test can detect every carcinogen. Salmonella is pretty good. The organic chemicals that are known to cause cancer in people are virtually all detected by the Ames test. Metal carcinogens are not detected by this system.

"The system also seems to do rather poorly with some classes of carcinogens. Some chlorinated chemicals were mentioned this morning. There are some others.

"Some of the other methods do detect these chemicals. In fact, when you put together several short-term tests and look at the list of chemicals that cause cancer in people and look at the list of the hundreds of chemicals that cause cancer in animals, you can detect virtually all of them using a combination of short-term tests, so there is a complementarity among short-term tests that I think makes a battery essential, makes using more than one test essential because of the danger of missing things, of having the so-called false negatives.

"The other reason, I believe, is that there is certainly the theoretical possibility of making mistakes in the other direction any time you use a test that is different from what you are basically interested in, which is that we are interested in people ultimately.

* * * * *

"Now, a battery in my view contains a number of different forms. The way I like to think about it is that in general, the less data we gather, the more likely we are to miss something. So that technically, we could make a list that would maybe contain 10 or 12 short-term tests and say, "This is absolutely the best we can do and this gives us the greatest assurance in detecting something that might be hazardous," and then as we pull back from that, I think the risk of making a mistake has to go up a little bit.

"And how much one is willing to have that risk go up I think depends enormously on what the potential health hazard is, which comes down quite often to the degree of exposure to people.

"So I think of batteries being of different sizes, depending upon the level of concern. In terms of a regulatory decision, I definitely feel that more than one positive result is required." (McCann, Tr. 1562–1563, 1564–1565)

Dr. David Brusick (AIHC) also recommended a battery:

"(b) A single test response is probably insufficient to be of value in carcinogen identification. A consistent trend of responses among a reliable battery of at least four SST would be necessary to reach a conclusion regarding genetic activity. The battery should consist of tests which detect specific locus gene mutation and chromosome aberrations. The group of assays given in Tables 1 and 2 represent an acceptable battery." (Brusick, S. 15)

Other witnesses who expressed similar opinions were Dr. Renate Kimbrough (CDC), Tr. 1795; Dr. Benjamin Van Duuren (NYU), Tr. 1868–1869; Dr. Lawrence Fishbein (NCTR), Tr. 1886–1888; Drs. Curtis Harris (NCI) and Benjamin Trump (Univ. of Maryland), Tr. 1975–1984; Dr. Roy Albert (EPA), Tr. 2380; and Dr. Geoff Taylor (NIOSH), Tr. 2945–2946.

The CIIT Workshop on "Strategies for Short-term Testing for Mutagens/Carcinogens" also recommended using a battery of validated short-term tests:

"The Workshop concluded that results from a battery of validated tests could be of significant value in assessing the carcinogenic potential of a chemical, provided that the overall assessment was made in the context of a rational examination of all the facts concerning the compound. Positive results in several, valid short-term tests indicate that, without waiting for the results of long-term animal exposure studies, operations involving the chemical should be immediately examined and human exposure reduced to as far as is practicable . . . The results of lifetime animal exposure studies would be extremely valuable in confirming carcinogenic potential of a chemical and in establishing acceptable safe limits of exposure, and such studies should be considered. Nevertheless, positive results from an adequate short-term testing battery cannot be ignored and an effective program to protect people who are likely to be exposed should be instituted without delay.

"A further suggestion in formulating a battery of tests would be to incorporate at least one system that involves the use of mammals or mammalian cells. Also, many investigators felt that cell transformation systems showed the most promise as accurate predictors of the carcinogenic potential of chemicals." (Golberg, S. i–vi i–v.)

IARC also recommended the use of a battery:

"The present state of knowledge does not permit the selection of a specific test(s) as the most appropriate for identifying potential carcinogenicity. Before the results of a particular test can be considered to be fully acceptable for predicting potential carcinogenicity, certain criteria should be met: (1) the test should have been validated with respect to known animal carcinogens and found to have a high capacity for discriminating between carcinogens and noncarcinogens, and (2) when possible, a structurally related carcinogen(s) and noncarcinogen(s) should have been tested simultaneously with the chemical in question. The results should have been reproduced in different laboratories, and a prediction of carcinogenicity should have been confirmed in additional test systems. Confidence in positive results is increased if a mechanism of action can be deduced and if appropriate dose-response data are available. For optimum usefulness, data on purity must be given.

* * * * *

"An adequate assessment of the genetic activity of a chemical depends on data from a wide range of test systems. The monographs include, therefore, data not only from those already mentioned, but also on the induction of point mutations in other systems [61–66], of structural [67] and numerical chromosome aberrations, including dominant lethal effects [68], of mitotic recombination in fungi [61] and of sister chromatid exchanges.[69,70]." (IARC, 1978, Vol. 17, p. 27, footnotes omitted)

The EPA has also proposed to require the use of a battery of short-term tests in the evaluation of pesticides for chronic hazards. In the "Proposed Guidelines for Registering Pesticides in the U.S.; Hazard Evaluation: Humans and Domestic Animals", EPA provided a basis for the use of a battery of short term mutagenic assays:

"In developing these proposed guidelines, EPA and the study group relied on certain well established principles of genetic theory.[13] The most important points are: That essentially all organisms contain DNA as their genetic material; that the DNA genetic code is universal among life forms; that mutations occur spontaneously in all living beings; and that the frequency of mutation can be increased by exposure to chemicals. These basic points mean that all species can be used to detect and predict genetic change in other species. Thus, the Agency can use mutagenicity data from test systems which employ many different life forms to assess the potential of chemicals to produce mutagenic effects in humans." (43 FR 37348, footnotes omitted)

EPA described its guidelines as follows:

"The proposed mutagenicity guidelines contain a "battery" of 13 different kinds of tests which are grouped into three different categories. Two of the categories would be designed to evaluate the two large categories of genetic abnormalities: Gene mutations and chromosome aberrations. A third category of test would evaluate the potential of a chemical to interact with or to cause primary damage to DNA or other genetic processes in a cell. These tests detect a potentially broader spectrum of genetic events than do gene and chromosomal mutation tests.

"An Applicant would be required to submit data from several kinds of tests in each category: Three kinds of gene mutation tests, three kinds of chromosome aberration tests, and two kinds of DNA damage/repair tests. Data would be required therefore, from a total of eight different kinds of tests. EPA proposes to require several kinds of tests from each of the different categories because it is unlikely that any single test system is adequate to evaluate with sufficient sensitivity the full range of genetic damage which could be caused by a chemical. Nor is

it likely that any one test system is sensitive to the entire variety of chemicals used as active ingredients in pesticides. Finally, one other advantage of the battery approach is that applicants have considerable flexibility in the timing and selection of tests." (43 FR 37348)

It should be recognized, however, that EPA's proposed requirement of eight tests is made in the context of safety testing. Although negative results in eight tests may be needed to provide reasonable assurance of safety, positive results in as few as two would give a high degree of confidence that a chemical poses hazards.

As described above, OTA reviewed results in ten short-term tests in the evaluation of the carcinogenicity of saccharin. A NAS report on the *Principles and Procedures for Evaluating the Toxicity of Household Substances* also recommended the use of a battery of short-term tests:

"Mutagen tests must fulfill certain requirements if they are to provide information suitable for the protection of humans. No single extant test meets each of the requirements; therefore, a combination of tests must usually be employed, as exemplified above.

"The full spectrum of molecular classes of mutation must be detectable. These include the loss or gain of entire chromosomes; mutations arising from chromosome breaks (or equivalent events) namely deletions, duplications, and rearrangements; and point mutations. The last consist of chromosome mutations that are small enough to affect only a single gene, of additions or deletions of one or a few base pairs, and of base pair substitutions. Criteria for reliably detecting all types of point mutations are notably lacking in the in vivo mammalian test systems.

"Many nonmutagenic chemicals become mutagenic as a result of metabolic processing. Conversely, some mutagens may be so efficiently inactivated through metabolic action that they become innocuous. Thus, an understanding of the corporeal pharmacology of environmental chemicals is crucial to mutagen testing.

A suitable capacity for metabolic activation must be incorporated into any test system other than the intact animal. Two methods are currently available. The first involves the direct incorporation of enzymatically competent mammalian tissue extracts into microbial tests (including cultured mammalian cells). The second involves administering the agent to an animal and then obtaining animal extracts (such as urine or blood) for subsequent analysis in a microbial test. Metabolic activation systems are also under continual development. Improvements are to be expected on a regular basis for a number of years.

"The pharmacological importance of such factors as routes of administration should not be underestimated. For example, some intestinal organisms contribute to the mutagenic activation of certain chemicals; therefore, it is important that the routes of exposure be appropriate.

"Finally, test systems must display both sensitivity, detecting as broad a spectrum of chemical classes as possible, and accuracy, including reproducibility." (NAS, 1977c, p. 89)

Finally, a report prepared for DHEW by the Subcommittee on Environmental Mutagenesis recommended a battery of short-term tests:

"The report presents a critical evaluation of a number of tests which have been utilized in research laboratories. Because chemicals may induce mutations which affect different levels of organization of the genetic material, this discussion is partitioned to test systems which detect: 1) breakage or rearrangements of parts of chromosomes; 2) chemical changes in single genes; and 3) more subtle chemical changes in the DNA. Because a single test system will not detect all types of events with a high degree of accuracy, the report stresses the need for using a battery of tests when attempting to assess the mutagenic potency of a chemical.

* * * * *

"For chemicals which receive widespread human exposure (e.g., food additives, certain pesticides), an extensive battery of genetic tests may be necessary. This battery could be appropriately modified based upon the availability of other toxicological data on a particular compound. For limited human exposure (prescription drugs), test systems would be selected which would reflect knowledge of the chemical's structure and properties, use levels, and the population at risk.

"In situations where a large number of chemicals must be tested for mutagenicity, it may not be feasible to put them through an entire battery of tests simultaneously. One approach to this is a hierarchical or tier system which employs a prescreen step. The purpose of this step is to rapidly identify those substances which are genetically active and it routinely employs a sensitive, rapid, method using bacteria (the Ames test is one such method).

* * * * *

"Continuing to stress the need to employ a battery of tests, the Committee further discussed procedures which are necessary to define a chemical as a human mutagen. In providing such optimal criteria, it is again stated that practical procedures to assess the induction of heritable mutations directly in humans are not currently available. The list presented reflects the current state of the art and may be altered as improvements in methodology and advancement of knowledge accrue." (DHEW, 1977, p. 304)

Again it should be recognized that the recommendation for an "extensive" battery is made in the context of testing to establish safety.

Although a battery of short-term tests was highly recommended to OSHA, very little comment was offered on what guidelines OSHA should adopt in how to use the battery. The design of an appropriate battery or the interpretation of the results from a battery received very little comment in the Record of these hearings. One witness who did comment was Dr. David Rall (Director, NIEHS). Dr. Rall referred OSHA to the DHEW Subcommittee Report on Environmental Mutagenesis and suggested that OSHA adopt the subcommittee guidelines on how to interpret results from mutagenic assays. Dr. Rall continued:

"The field, as I am sure you know, is moving very rapidly. The tests are becoming much better validated, more sophisticated. We are trying to develop ways where they can be almost automated with excellent quality controls. These results are coming out now, and I think in the next year or so we will have a very much better picture of which of this myriad of tests—and there are about thirty—are the most reproducible and the most reliable. And I think the longer OSHA or anyone waits to set their criteria for acceptance of tests in place, the smarter they are. The field is moving very rapidly.

"If you wanted to pick a few tests now, sure, you could pick them, but I would rather wait until we have a little more data which is coming out and do it then." (Rall, Tr. 368)

Dr. Lawrence Fishbein (NCTR) also expressed the opinion that OSHA should not move too quickly to establish criteria or standards for the battery of tests which should be used. When asked how many short-term tests should provide positive results before weight should be applied to those results, Dr. Fishbein responded:

"I would not want to place a specific number. I would think a positive in perhaps two tests, the Ames and the transformation of mammalian cells in vitro, would do it . . . one mammalian and one microbial." (Fishbein, Tr. 1888)

7. Would the regulation of carcinogens which are also mutagens provide additional benefits by reducing mutagenic hazards?

An important consideration which was not addressed by many witnesses was whether carcinogens pose a mutagenic risk to exposed humans. Since there is little scientific argument against the conclusion that most carcinogens are also mutagens, protection of workers from the mutagenic effects of carcinogens that are also mutagenic would be an additional benefit from the regulation of carcinogens. Dr. Robert Squire (Johns Hopkins Univ.), citing the *DHEW Report on Approaches to Determining the Mutagenic Properties of Chemicals* commented:

"A major concern other than for cancer is over the potential of genotoxic chemicals to induce genetic alterations in future generations. In 1977 the DHEW

Subcommittee on Environmental Mutagenesis (1977, pp. 309–310) reported:

"There is no known way to estimate the contribution of chemical agents to the human genetic disease burden, either as it exists now or as it is likely to exist in the future. Concern over the possibility that certain chemicals may pose a threat to the integrity of the human genome (the totality of genes comprising the chromosomes) and thus to future generations of humans is predicated on sound theoretical reasoning and inescapable implications derivable from a large body of contemporary knowledge. While proof is lacking, there can be no reasonable doubt that man has endured through thousands of generations despite the presence of mutagenic agents in the human environment. In the recent past, as a result of the industrial revolution, the spectrum and number of agents has increased markedly. Although we still have extensive exposure of the human population to numerous natural mutagens, we now have, in addition, exposure to numerous man-made chemicals, many with potent mutagenic activity. This new type of exposure may well have increased the amount of damage in the present human population. Thus, the need is to devise, develop and utilize test approaches which identify mutagenic potential, assess potency, and provide results which are understandable in terms of the human responses as part of the toxicologic, safety evaluation process . . .

"The fundamental concern in mutagenesis is the risk to future generations. Alterations of the genetic material in germinal cells are seldom expressed in the exposed individuals and indeed, may not be manifest for several generations. Since gametogenesis requires both mitotic and meiotic processes, assessment of mutagenicity should ideally involve testing of cells which undergo meiosis. Nevertheless, the usefulness of cells other than germinal cells as a predictive tool is judged to be high, particularly for certain kinds of genetic alterations." (Squire, S. 10)

Dr. McCann also expressed the opinion that controlling mutagens was an important additional benefit from controlling carcinogens:

Critically examining the value of short-term tests only with respect to their relevance to cancer is somewhat artificial in that chemicals that cause mutations are of interest whether or not there is evidence they also cause cancer. Mutagenic damage to the human gene pool could itself be an important problem. There is a relatively high incidence of birth defects (5–10 percent of all children in the U.S. are born with birth defects). The number and amounts of chemical mutagens in the environment (both natural and man-made) indicate the role of chemical mutagens in causing birth defects could be substantial. There is also some suggestion that DNA damaging chemicals play a role in causing atherosclerosis, the main form of heart disease. It may be that cancer is simply one disease manifestation belonging to a more general class of adverse health effects that can result from DNA damage. If such damage occurs in the germ line (egg or sperm cells) then hereditary damage, such as birth defects* can result. If mutations occur in the somatic cells, for example in lung tissue, then cancer can result. The complete story is not known, and is no doubt quite complex. There are most certainly other physiological processes involved which contribute to the development of these health problems. However, the data now at hand indicates that it is very likely to the clear advantage of society to locate the primary sources of human exposure to mutagens, and as much as is feasible, to make it possible for individuals to limit their exposure (McCann, S. 12–14).

Dr. Lawrence Fishbein (NCTR) commented that carcinogens do pose a mutagenic risk to humans:

"I think that there is an obvious potential genetic hazard for known chemical carcinogens and mutagens." (Fishbein, Tr. 1886–1887)

He expressed the opinion that if carcinogens are regulated in such a way as to reduce human exposure then it would be beneficial to reduce mutagenic human risk.

Dr. Arthur Upton (Director, NCI) also expressed a concern for the genotoxic nature of many carcinogens:

"The short-term test may help us in determining that the substance in question is, in fact, genotoxic, is capable of attacking the genes of the cell. We know there is a very high correlation between genotoxicity or mutagenicity and carcinogenicity." (Upton, Tr. 290)

EPA in its proposed pesticide guidelines also discussed how regulating mutagens would also provide the obverse benefit of protecting against carcinogenic risks:

"The Agency, of course, recognizes the long-term significance and potential benefits of selected mutagenicity tests in oncogenicity screening. In particular, the correlation between results from submammalian gene mutational tests, such as the Ames test, and results from in vivo bioassay techniques for oncogenicity, is an area under active scientific consideration. EPA emphasizes, however, that the proposed testing requirements relate only to the assessment of mutagenic effects. Regulatory use of mutagenicity testing to evaluate oncogenic effects must be considered in its own right." (43 FR 37347)

C. OSHA's Conclusions

On review of the evidence cited above, OSHA recognizes that there was a wide range of opinion among the witnesses about the reliability and significance of short-term tests. However, much of the opinion was unsubstantiated, and sought to persuade OSHA not to regulate a substance as a potential occupational carcinogen based solely on short-term tests. Reviewing the testimony of the scientists who are specialists in the area (Drs. McCann, Brusick, Hart, Fishbein, Trump, Harris, and Meselson) and the specific studies which have investigated the validity of the test systems (McCann *et al.*, 1975; Purchase *et al.*, 1976; Sugimura *et al.*, 1976; and other papers cited in Brusick's testimony), OSHA is impressed by the weight of evidence that such tests provide meaningful results and that substances which give positive results in the well validated systems are likely to be carcinogenic. OSHA notes also that this conclusion was supported by representatives of agencies such as EPA, NIEHS, and DHEW. Thus OSHA concludes that there is ample justification for the use of short-term tests for the limited purpose of providing confirmatory evidence for a single otherwise uncorroborated animal bioassay. On the evidence presented in the Record, the probability of a false positive result for a chemical which is positive in one well-conducted bioassay and one well-validated short-term test is extremely small. In general, OSHA intends to rely upon at least two positive results in different test systems to provide this type of confirmation. This Part also defines five such systems, which, based upon the discussion above, OSHA believes are sufficiently validated to utilize as concordant evidence. Moreover, OSHA recognizes that the evaluation of positive results in short term tests is a matter for good scientific judgment and will interpret the data on each substance on their own merits. As further systems become validated, OSHA intends to amend this Part accordingly. Some participants claimed that where a substance has given positive results in two or more short-term tests in the absence of any long-term testing in mammalian systems, that such evidence would be concordant with other evidence of potential carcinogenicity. Although two of the most experienced and informed witnesses at the hearing expressed the opinion that such evidence should suffice for regulation of the substance as a Category I toxic substance, OSHA recognizes that the majority of the scientific opinion at the hearing would not support such a regulatory principle at the present stage of development and validation of the tests. However, OSHA is impressed by the consensus of scientific opinion expressed in the introduction to the CIIT Workshop that:

"Positive results in several, valid short-term tests indicate that, without waiting for the results of long-term animal exposure studies, operations involving the chemical should be immediately examined and human exposure reduced to as far as is practicable." (Golberg, S. i–vi)

VII. Structural Similarity to Known Carcinogens

A. OSHA's Proposal

In the preamble to the proposed regulation, OSHA stated that: "In determining whether a toxic substance poses a carcinogenic risk to humans . . . OSHA will not, at this time, place . . . any reliance on molecular structure or similarity . . ." (42 FR 54155). OSHA explained its reluctance to use molecular similarity to known carcinogens for purposes of regulating exposure to possible carcinogens as follows:

"Whether chemical similarities between known carcinogens and other untested substances should be used to qualitatively predict the carcinogenic effects of those untested substances, as a matter of regulation, rather than of research, has been debated in recent time."

"OSHA is aware that, for many years, priorities for scientific research in testing individual substances for carcinogenic activity have sometimes been set, to a certain extent, by the structural similarity of those substances to be tested to the structural similarities of other substances that have been tested and found positive for carcinogenic activity. This concept has often been referred to as the "structure/function" theory. Many have recognized the distinction between using structural similarity to predict carcinogenic activity of an untested substance as a basis for setting priorities when actually testing substances on the one hand and using such structural similarity to regulate untested substances that may have a great deal of structural similarity to substances that have been tested and found positive on the other hand." (42 FR 54168)

OSHA similarly declined to consider substances safe from suspicion of carcinogenic hazard based on chemical structure. The Ad Hoc NCI Committee's report to the Surgeon General was cited in the preamble to the proposed regulation as follows:

"At the present time the chemical structure or physico-chemical properties of a compound do not provide a reliable basis for prediction of freedom from carcinogenic activity. Several structure-activity correlations are valuable indicators of the possible carcinogenicity of a compound but none can be used to classify the compound as noncarcinogenic." (NCI Ad Hoc Committee, 1970, p. 5–6)

OSHA concluded by stating, ". . . at least at this time, OSHA does not propose to rely upon structural similarities between known carcinogens and other substances to regulate those other toxic substances as carcinogens. Public comment as to this specific part of the proposal is invited." (42 FR 54168).

B. The Public's Response and OSHA's Evaluation

The issue of whether chemical structure can play a role in the identification, classification and regulation of potential carcinogens was discussed by several witnesses in this proceeding. A related topic discussed by several participants, was whether potential carcinogens, particularly inorganic compounds, can be grouped into classes on the basis of structural or chemical similarity and regulated together. Comments both in favor of and opposed to use of chemical structure as a guide to predicting carcinogenicity were submitted. While no clear consensus of opinion was reached, a preponderance of witnesses, including several experts testifying for industrial interests, favored at least some role for chemical structures in the OSHA procedures for identifying and regulating carcinogens.

Witnesses supporting use of chemical structures in classifying toxic substances as carcinogens included Dr. Fishbein, (NCTR), Dr. Van Duuren (NYU), Dr. Lijinsky (NCI–FCRC), Dr. Squire (Johns-Hopkins), Dr. Saffiotti (NCI), Dr. Shubik, (Eppley Institute, Univ. of Nebraska), Dr. Roe (AIHC), Dr. Goldman (Harvard Univ.), and Dr. Harris (Uniroyal). Other witnesses, Drs. Rogers, Furst, and Powers (Brush Wellman), testified that they opposed any use of structural similarity to provide a basis for regulation of possible carcinogenic substances, while the comments submitted by NIOSH indicated support of a role for molecular structure depending on whether the compounds in question were organic or inorganic in nature. These expert opinions are reviewed in greater detail below.

Dr. Lawrence Fishbein (NCTR) singled out OSHA's original rejection of the utility of chemical structures in classifying potential carcinogens as an area of "particular concern." Dr. Fishbein stated:

"OSHA is to be commended for its proposed regulation to protect workers from occupational exposure to carcinogens. However, certain parts of the policy trouble me. One area of particular concern is the failure to make use of information on structural and metabolic similarity to known carcinogens. Other agencies, such as EPA, have stated their intent to use "structural similarity" at least to set priorities, if not to regulate chemicals under the Toxic Substances Control Act (TSCA). In OSHA's Cancer Policy information of this type could be incorporated into both Category I and II Criteria. Just how this information could best be utilized is open to debate. I feel the combination of positive results in one well-conducted animal test and structural similarity to a known carcinogen or group of carcinogens would be sufficient to place a chemical in Category I. The suggestive evidence required for Category II could be satisfied with multiple short term tests and structural similarity to a known carcinogen or group of carcinogens. To foreclose any consideration of the growing body of structural and metabolic information would be irrational." (Fishbein, S. 6)

Dr. Fishbein also stated:

"There is an expanding literature to suggest that a critical examination of the chemical structure *per se*, reactivity, as well as aspects of biotransformation, can, in a number of instances, serve as a predictive tool for the assessment of potential carcinogenicity in laboratory animals and/or humans." (Fishbein, S. 3).

Dr. Fishbein pointed out that within certain groups of substances there is strong evidence that it is the common chemical moiety *per se* which imparts carcinogenicity. Among the chemical groups for which there is strong evidence of carcinogenicity for most or all of the compounds studied are: nitrosamines; alkylating and acylating agents; halogenated unsaturated derivatives; and aromatic amines, according to Dr. Fishbein (S. 3–4). During oral testimony, Dr. Fishbein explained further why chemical structures would be useful for predicting carcinogenicity in particular situations:

"Some classes [of compounds] give you more confidence than others by dint of the volume of information that has been accumulated, such as halogenated olefins, aziridines, nitrosamines, where there are many, many examples of carcinogens. So that the introduction in the future of a compound related to those compounds would certainly raise in my estimation a very high probability of a risk, solely based on the data that is available of similarly related compounds" (Fishbein, Tr. 1819).

Dr. Fishbein emphasized that informed scientific judgment is necessary to evaluate the likelihood that a chemical is carcinogenic by dint of its molecular similarity to known carcinogens.

"Q. Could you tell me what qualifications would be required to make this type of determination?"

"A. Well, a chemist with a number of years' experience, an organic chemist who is familiar with the literature of carcinogenic and mutagenic compounds, who has familiarity with metabolic routes. I think these attributes would be a requirement." (Fishbein, Tr. 1825)

Dr. Van Duuren (NYU) agreed with Dr. Fishbein that chemical structures can be informative about the likelihood that a compound has carcinogenic properties. Dr. Van Duuren wrote:

"The chemical structure of a compound can frequently serve as a guide to potential carcinogenicity in animals or humans." (Van Duuren, S. 3).

Dr. Van Duuren provided several specific examples of cases where carcinogenicity was indeed predicted by research scientists on the basis of molecular structures. Dr. Van Duuren wrote:

"The compounds chloromethyl methyl ether (CMME), bis(chloromethyl)ether (BCME), and trichloroethylene (TCE) are classical examples of the utility of such information. I selected CMME and BCME on the basis of their chemical reactivity from a list of over 400 chemicals handled by one chemical manufacturer. Their structures suggested that the halogen atom would be very reactive in displacement reactions. The existence of resonance forms involving carbonium or oxonium ions would allow nucleophilic displacement of the halogen bearing carbon atom. This has been shown to be a typical reaction of a-haloethers. Because of this they fall into the broad category referred to as alkylating agents, many of which have proven to be carcinogenic, e.g., epoxides and ethylenimine. Subsequent studies in mice exposed by the dermal and subcutaneous routes and in rats [exposed] subcutaneously bore out our initial assumptions. The bifunctional alkylating agent, BCME, was shown to be carcinogenic in both test systems and also a potent initiating agent in two-stage carcinogenesis. CMME although inactive alone, showed significant activity in 2-stage mouse skin carcinogenesis.

"A third example is TCE. On the basis of several known metabolites in humans, we proposed a metabolic pathway involving an epoxide intermediate. This, in addition to its structural similarity to vinyl chloride (a potent liver carcinogen), led to the prediction that TCE would be carcinogenic, which was proven correct by the recent NCI bioassay. TCE was shown to be carcinogenic by feeding in B6C3F1 hybrid mice. More recent biochemical studies have provided evidence supporting our initial prediction on TCE's metabolic fate.

"In addition, work done in our laboratory with the monofunctional epoxides, epichlorohydrin and styrene epoxide, has pointed to the importance of a reactive adjacent functional group for carcinogenic activity. Our predictions on these two compounds were confirmed in subsequent animal testing. From these and other studies, reliable criteria for predicting carcinogenic potential have been developed. These include:

1. Functionality (mono-, bi-, etc.)
2. Interatomic distances in bifunctional agents
3. Stereochemistry
4. Molecular flexibility in bifunctional agents
5. Chemical reactivity with nucleophilic reagents
6. Known or suspected metabolic pathways.

"From the above examples it is obvious that data on chemical structure should not be disregarded, as is proposed by OSHA." (Van Duuren, S. 3–5, references omitted)

Dr. Van Duuren further agreed with Dr. Fishbein that informed scientific judgment is necessary to evaluate the likelihood that a chemical is a carcinogen by virtue of its structural similarity to known carcinogens:

"* * * the inclusion of structural considerations into regulatory decisions cannot be reduced to a formula and will require good scientific judgment." (Van Duuren, S. 5)

In his comments on the usefulness of considering chemical structures in protecting employed persons from exposure to possible carcinogens, Dr. Van Duuren wrote:

". . . I believe that current scientific knowledge can support the use of chemical structure analysis in predicting the likelihood of chemical carcinogenesis in certain situations. Such information would be useful to OSHA in determining the classification of various toxic substances and, therefore, should be incorporated within the regulation." (Van Duuren, S. 8–9)

Dr. Van Duuren added:

"I agree that evidence of structural similarity to a known carcinogen would not stand alone in determining whether a compound is carcinogenic. However, it would seem reasonable that structural similarity in combination with positive results in one mammalian species or in several short-term tests would be sufficient evidence for a Category I classification or at least Category II." (Van Duuren, S. 5)

During oral testimony, Dr. Van Duuren testified:

"* * * the proposed [OSHA] document does not give that much weight to a structure activity, * * * we should consider very seriously the chemical structure and its possible biological activity * * *

"If we are dealing with direct-acting carcinogens, and by that I mean alkylating agents, acylating agents, we should be very much concerned about those compounds. In the case of indirect-acting agents which have to be metabolized, we should consider possible metabolic pathways and what intermediates might be involved, and where these intermediates will be activated carcinogenic intermediates." (Van Duuren, Tr. 1835)

Dr. William Lijinsky (NCI–FCRC) emphasized that many of the known chemical carcinogens belong to well-defined chemical classes which can be recognized by information on structures. Dr. Lijinsky mentioned three such chemical classes in his testimony:

"There has been an explosion of work in chemical carcinogenesis during the past twenty years or so and a large number of compounds have been found to induce cancer in experimental animals, many of them belonging to a few well-defined chemical classes. Among them are polynuclear hydrocarbons, aromatic amines and N-nitroso compounds. It is noteworthy that many of these carcinogens were considered safe (i.e. noncarcinogenic) before they were tested in animals, although the grounds for making such an assumption are obscure." (Lijinsky, S. 7)

Dr. Umberto Saffiotti (NCI) and Dr. Robert Squire (Johns Hopkins Univ.) stated that structural information should be used in conjunction with other data in classifying toxic substances. Dr. Saffiotti mentioned "special cases" where a combination of evidence could be sufficient to place a substance in Category I:

"An example could be that of a substance for which a single test in mammalian species is overwhelmingly positive, the compound is a close chemical analog of a group of well established carcinogens, and there is incomplete but highly suggestive evidence of effects in humans or in another species." (Saffiotti, S. 38)

In one of his exhibits, Dr. Saffiotti gave an example of the relationship between knowledge of structure-activity relationships and the adequacy of biologic systems in which the activity is measured:

"The manner in which the chemical aspects of carcinogenesis are evaluated in biological terms has sometimes caused me some concern. One of the major problems in attempting to assess the pathways for chemical activation of carcinogens and in identifying ultimate carcinogens consists of relating chemical structure to the long-term biological effect that characterizes a given chemical as a carcinogen, i.e., the induction of tumors. Let me use, as an example, the compound dibenzl[a,c]anthracene, a five-ring aromatic hydrocarbon without K region. It was first bioassayed by repeated skin applications in mice during the initial studies on the carcinogenicity of polynuclear hydrocarbons in the early 1930s (2). In a first series of skin tests, an impure preparation was tested in a total of 60 mice, of which only 17 survived at one year; the only two mice which survived over 600 days developed skin carcinomas. A purer preparation was tested in 10 mice, of which two survived over 600 days and one developed skin carcinoma. In a subsequent test using a pure sample, only 20 mice were used, only two survived at one year, the last mouse dying at 487 days, and no tumors were found. The authors went on to state: "we cannot say that no tumors would have been obtained had the mice lived exceptionally long, as in the earlier series with the impure material." However, in their discussion, the compound was considered noncarcinogenic and this classification was accepted, without further tests, by other authors. The compound was tested again in a similar way in a group of 15 mice by Heidelberger et al. (3) in the early 1960s and, since again no tumors were observed, the authors confirmed its lack of carcinogenicity: on this basis, the compound was later used as a "negative control."* Van Duuren et al. (4)

then tested it, but just for initiating activity on mouse skin. They found it positive and therefore called it a noncarcinogenic initiator. We tested it (5) for full carcinogenic activity on mouse skin and found it quite active as a full carcinogen, although with a long latent period (eight carcinomas out of 30 initial mice, average latent period of 60 weeks). DiPaolo et al. have shown (6) and he has reported here (7), that this carcinogen induces neoplastic transformation in vitro. The important point that I want to stress by this example is that our knowledge of the carcinogenicity of a given chemical structure is a reflection of the biologic systems by which we determine carcinogenicity. A critical evaluation of these bioassay systems and of their sensitivity is needed in defining the biologic activity (or lack of activity) of a given chemical." (Saffiotti, 1974, pp. 729–730; Exhibit to Saffiotti Statement)

Dr. Squire mentioned that chemical structures could furnish regulatory information, but only if used in conjunction with other data:

"I do agree, that structure-activity predictions ought not to be used *by themselves* to classify a substance as carcinogenic or noncarcinogenic." (Squire, S, 30, emphasis added)

Statements of witnesses invited by industry included several opinions that chemical structure information should indeed be used by OSHA in classifying toxic substances as carcinogens. Dr. Phillippe Shubik (Eppley Institute, Univ. of Nebraska) quoted the OSHA Proposal:

" '(OSHA) will not place any reliance on molecular structure * * *' "

and commented:

"Surely this is somewhat extreme. It is accepted that specific chemical structures, *e.g.* aromatic amino groups, polycyclic aromatic hydrocarbons, the nitroso groups, tend to confer carcinogenicity on a molecule * * * thus, a complete failure to use structure-activity relationship is totally irresponsible." (Shubik, S. 11)

Dr. Francis Roe (AIHC) also stated that OSHA's original proposal not to take chemical structures into account in classifying chemicals for regulation should be modified. Dr. Roe wrote:

"* * * extrapolation to man should not, as seemingly proposed by OSHA in their 11 principles, be based solely on a consideration of the results of a long-term animal test. All available information should be taken into account, including chemical structure. * * *" (Roe, S. 71, emphasis omitted)

Dr. Roe added:

"* * * there are some chemical structures about which, even in the absence of any biological data, I should be very concerned." (Roe, S. 85)

Dr. Peter Goldman (Harvard Univ.) similarly advocated some role for information on chemical structures when he wrote:

"It is the structural properties of the carcinogen which determine its pathway of activation, and our knowledge of structural similarities enables us in many cases to predict which pathway will be followed for the activation of a particular compound." (Goldman, S. 12)

Additional testimony supporting a role for chemical structure information in identifying potential carcinogens was furnished by Dr. Walter Harris (Uniroyal). Dr. Harris related the attempts of his laboratory to design a miticide with the benefits of "Aramite" but without its carcinogenic activity. (Tr. 7394) He testified:

". . . we selected the best [miticide] and ran a full-scale, two-year animal (carcinogenicity) study. Because of the chemical relationship to "Aramite," we knew we had to put it to a very rigorous test . . . when the first few animals were sacrificed . . . they were full of cancer. We simply stopped right there and went back to the bench . . . There is a happy ending . . . we learned what part of the chemical structure caused cancer, and . . . create[d] a new chemical which does not cause cancer in animals yet controls the mites . . .". (Harris, Tr. 7395)

Testimony opposing any use whatsoever of chemical structures as predictors of possible carcinogenic hazard was limited to that of Dr. Arthur Furst (Univ. of San Francisco), Dr. Adrianne Rogers (MIT) and Mr. Robert Biggs (Brush Wellman). Dr. Rogers wrote:

"From a scientific point of view, it appears that the question of carcinogenicity should be considered separately for each element, compound, mixture, alloy or other material, and that tests of a material of one structure and composition cannot be used as a basis for drawing conclusions of carcinogenicity of materials of different composition or structure because they have one or more components in common. The definition of "toxic substance" should be clarified to include only the specific material tested and found to be carcinogenic." (Rogers, S. 9).

During cross-examination, Dr. Rogers repeated her opinion as follows:

". . . [T]ests of a material of one structure and composition cannot be used as a basis for drawing conclusions of carcinogenicity of materials of different composition or structure simply because they have one or more components in common". (Rogers, Tr. 5566]

Dr. Furst similarly opposed use of chemical structure information for regulation, and provided examples of why he considered such information to be unreliable for both organic and inorganic compounds:

"The (OSHA Proposal) discusses the aspect of chemical similarities as a means of predicting potential activity of untested compounds. In many, if not most cases, the actual research must be done . . . Butter yellow dye produces hepatomas when fed to rats; the 4'–F [derivative] is also active, the 2-OH is not.

"There is a tendency for many scientists who have not done actual laboratory research in metal carcinogenesis to lump all compounds of an element together. As noted in my publication (Furst, A, & Schlauder, M. J., Environ. Toxicol. and Path. 1, 51 (1977), silver fails to produce tumors under the most favorable conditions to test a compound as a carcinogen, yet in two of my references, silver is listed as being carcinogenic. In a new publication of mine (Furst, A., J. Nat. Cancer Inst., May (1978)), I show an organic manganese compound active in rats. The pure element manganese and the dioxide under identical conditions are inactive, thus manganese cannot be called a carcinogenic element. Again as quoted in one of my publications (Furst, A., Schlauder, M. and Sasmore, D.P., Cancer Research (1976)), we found lead chromate and lead acetate to be active, but not lead metal or lead oxide.

"From this discussion I believe that each compound, element, or agent, regardless of similarity to a demonstrated carcinogen, must be considered as a separate entity and must not be classified as a group. Otherwise we will regulate many compounds in element classes as carcinogenic, when only one compound is active. Also we will rule out whole families of compounds—for example all hydrocarbons, all azodyes, all nitroso compounds. This is neither logical nor scientific." (Furst, S. 27–28)

In his prepared oral statement, Dr. Furst discussed some examples of inorganic substances which, in Dr. Furst's opinion, showed that structural considerations can be misleading:

"I am of the firm belief of the necessity to evaluate each discrete element, compound, alloy or other chemically or structurally distinct material individually for its potential carcinogenic action in animals.

"In the Federal Register of Tuesday, October 4, 1977, volume 42, . . . No. 192, page 54168, "Criteria for Identification"—Part D "Molecular Structure or Similarity," OSHA recognizes this important principle that it is not possible to use a structure/activity relationship to predict the presence or absence of the carcinogenicity of a new compound. This preamble uses as examples a number of different classes of organic compounds, which do indeed provide sound support for the position which the preamble takes. There is no mention in this section, however, of metals, alloys, metaleoids or inorganic compounds. Some persons, in particular representatives of NIOSH, have suggested at this hearing, that while it is scientifically sound not to extrapolate from one organic agent to another based on chemical or structural similarity, the same is not true of inorganic materials, and particularly not of metals. These persons have stated that if an organic element or one or more of its compounds are shown to be carcinogenic, all forms of the materials, including other compounds and alloys

containing it, should be deemed to be carcinogenic.

"No theoretical basis has been advanced for this distinction between organic and inorganic materials, nor could there be, for there is no sound basis for it. In fact there is a considerable body of empirical data to which my research has contributed, which demonstrates that the positive results of tests performed on certain elements, compounds or alloys are not indicative of carcinogenic activity in other compounds or alloys containing the same metal. For example, while certain forms of nickel including nickel powder, nickel carbonyl, nickelocene, and nickel subsulfide (Ni_3S_2) have reportedly induced cancer in animals, nickel monosulfide (NiS) under similar test conditions has not induced cancer. The use of the positive results with respect to certain nickel containing materials as a basis for drawing conclusions about other nickel containing materials would, in this case, result in the erroneous conclusion that nickel monosulfide is, and should be treated as a carcinogen.

"Still on the same subject of nickel containing materials, I recently ran a three year study comparing three nickel alloys called TRIP steels. Each contained about 8% nickel. Finely powdered samples were compared with pure nickel. No cancers of any kind were found in the TRIP steel treated rats; the rats treated with pure nickel had a statistically significant number of fibrosarcomas; the untreated vehicle control did not develop any tumor of the histological type.

"Manganese compounds provide another example. Bioassay work which I conducted under contract to the National Cancer Institute demonstrated that whereas manganese acetlyacetonate was carcinogenic, manganese powder and manganese dioxide exhibited no carcinogenic potential in parallel experiments. The report of this experiment, which was just published in the May, 1978 issue of the Journal of the National Cancer Institute, drew the conclusion that the results of tests conducted with a particular manganese containing material cannot be extrapolated to all compounds of that element, and that individual tests should be performed on each manganese containing material of interest before drawing conclusions concerning its carcinogenic potential.

"Lead and lead containing materials exhibit similar variations. We published in Cancer Research that lead chromate was carcinogenically active, but not lead metal or lead oxide. Others have published on the activity of lead acetate.

"A fourth example of the impropriety of grouping all compounds of an element as carcinogenic if one or two compounds of that element are active lies in OSHA's proposed treatment of beryllium containing materials. In the proposed beryllium standard, all beryllium containing materials were lumped together into one "substance" to be regulated as a single carcinogen. This is an example of the impropriety of extrapolating from one unlike substance to another. While there are reports in the literature that the element and certain of its inorganic compounds have induced tumors in animals, I can find no references which report that beryllium copper alloy has ever done so. I am making a thorough search of the literature for a new review I am writing. It is known that animal bioassay work has been done at NIOSH with dilute alloys of beryllium nickel and beryllium copper—the animals exposed to these agents did not develop tumors. The inability to make extrapolations from one material to another containing some of the same constituents, leads me to conclude that there is no scientific basis for postulating that beryllium copper alloy poses a threat as a tumorigen or a carcinogen. The only rationale, other than convenience, for extrapolating from beryllium compounds, such as beryllium sulfate to beryllium-copper would be that the elemental beryllium is the carcinogenic agent. In dilute beryllium copper alloys the beryllium exists in the alloy either in a solid solution or as a beryllide of the copper or cobalt. There is no known method at present of etching the elemental beryllium from the copper or vice versa. Metals in combination cannot be considered as the same physiological substances as the elemental metal.

"More recent research with metals indicates that under some experimental conditions, a metal may actually *inhibit* the action of a known carcinogen, be it inorganic or organic. Manganese inhibited the carcinogenic action of nickel subsulfide, a project completed by Dr. Sunderman under a contract for NIOSH. (Sunderman, *et al., Cancer Research 36,* 1790 (1976). Selenium inhibited the formation of colon tumors by 1, 2, Dimethylhydrazine (Jacobs, *et al., Cancer Letters 2,* 133 (1977), and finally, copper inhibited ethionine carcinogenicity (Brada and Altman, Adv. Exp. Med. Biol., 91, 193 (1977).

"In conclusion I believe that the term *substance* should be specifically defined as including only a specific, unique material, but not groups of similar or related materials; thus a 'toxic' substance within the meaning of the regulation would properly be limited to the specific, unique element, compound, or alloy, or other material tested by a valid experiment and found to be carcinogenic. Such a definition would comport with current scientific knowledge about the very limited extrapolability of results with one material to other materials similar in composition or structure" (Furst, Tr. 7151–7157).

Representatives from the Brush Wellman Company agreed with Dr. Furst that information on chemical structures should not be used by OSHA. "The Proposed Regulation," Brush Wellman wrote, deals with:

". . . the question whether chemical similarities between known carcinogens and other untested materials should be used as a basis for regulating the latter. Citing a number of circumstances in which small variations in composition or structure of different compounds or other materials can be determinative effects on carcinogenic potential, OSHA has tentatively concluded, and correctly so, that it will not rely on such similarities as a group for regulating materials . . ." (Brush Wellman, S. 3).

The NIOSH expert panel originally stated, in response to questions, that "similarity in structure cannot be used in an objective manner for regulation of chemical(s) as a Class I material" (Ex. 197, paragraph 29). However, during oral testimony, Dr. David Groth stated:

"If one or more inorganic nickel compounds were tested and found to be carcinogenic, then we assume that all the other inorganic compounds are also carcinogenic." (NIOSH, Tr. 3011)

* * * * *

"The fact that nickel sulfide has been found to be carcinogenic in rats by inhalation would indicate that nickel compounds in general are probably carcinogenic, and we would recommend that nickel compounds should be regulated as such.

"Now, I am not aware of any other nickel compounds that have been demonstrated to be carcinogenic—the nickel carbonyl by inhalation—other than that by inhalation. Other than that, there are some that have been shown to be carcinogenic by intramuscular injection as well.

"In general, I think that is correct. Once an opinion is made by the scientists who review the data that the nickel or whatever, metal salt, salts are carcinogenic, they can make a recommendation that the rest of the salts or inter-metallics or alloys will be also."

"If in fact, though, that someone were able to demonstrate something entirely different, I think that information should be evaluated, and perhaps at some time an exception might be made for one or more substances. (NIOSH, Tr. 3048)

Dr. Richard Niemeier clarified the NIOSH position on the usefulness of chemical structure information during oral testimony and stated that in the original NIOSH response to OSHA, quoted above:

"[NIOSH was] addressing organic compounds or organic substances, as opposed to inorganic substances * * * we are qualifying [the original NIOSH response to OSHA] to state an organic chemical instead of all chemicals . . ." (Tr. 3060–3061)

C. OSHA's Conclusions

On review of the scientific evidence presented at the public hearing, OSHA recognizes that its perceived position may not represent the consensus of scientific opinion found in the Record and perhaps should, therefore, be clarified or modified. The American Coke and Coal Chemicals Institute stated that:

"It is not clear in the proposal whether by 'toxic substance' or a 'potential occupational carcinogen' OSHA intends to mean individual chemical substances or combinations thereof as well." and "urge[d] OSHA to clarify its position on this matter in such a way as to reflect the complexities of actual situations". (P.H.C., Exh. 249, pp. 3–4)

In fact, there is substantial and documented evidence that for

substances that clearly fall into certain classes, strong inferences of potential carcinogenicity can be drawn on the basis of structural similarity alone. The chemical classes involved are primarily groups of organic chemicals, in which several members of the class have been shown to be carcinogenic and in which the activity can be associated clearly with a common chemical moiety or structural subunit (see the specific examples cited by Drs. Fishbein and Van Duuren). For substances in these classes, the presence of the chemical moiety in question may be useful in determining whether a substance should be identified as a potential occupational carcinogen. As explained by Dr. Fishbein, the critical factors involved in the use of this information are the experience and informed judgment of the scientists making the evaluation. Before using such information, OSHA will ensure that it is scientifically evaluated. Although OSHA is impressed by the opinion of Dr. Van Duuren that a chemical showing structural similarity to a group of known carcinogens, in combination with positive results in short term tests, should be classified into Category I, the scientific evidence does not justify adopting this as a general principle. On the other hand, it would clearly be imprudent to permit continued exposure of workers to a substance in a well-known class of carcinogens (e.g., alpha-haloethers, aziridines, or N-nitrosamines) while awaiting results of a long-term animal bioassay. In such cases, OSHA may regulate a group of substances on the basis of clear, positive evidence available on some members of the group. In hypothetical cases such as these OSHA intends to make use of expert scientific judgment, and the regulation as promulgated here provides sufficient flexibility to do so.

Certainly, OSHA intends to utilize such evidence in priority setting. Section 1990.132(b)(5) includes as one factor to be considered:

"Whether the molecular structure of the substance is similar to the molecular structure of another substance which meets the definition of a potential occupational carcinogen;

And OSHA has provided that one of the issues to be considered in the individual rulemaking is

"(a) Whether the substance, group of substances or combination of substances subject to the proposed rulemaking is appropriately considered in a single proceeding;" (§ 1990.146(a))

The issues raised by inorganic compounds are more complex, and OSHA recognizes that scientific opinion on these issues is less uniform. On the other hand, the issue of what constitutes "structural similarity" among inorganic compounds was not addressed in any depth by the witnesses in this proceeding and some of the apparent divergences in opinion appear to reflect different concepts of "similarity". It is clear from the testimony presented at the hearing that the mere demonstration of carcinogenicity of one compound of an element does not warrant the automatic inference of carcinogenic risks posed by all other compounds and mixtures containing the element. On the other hand, some of the examples cited by Dr. Furst and other witnesses as cases of "non-carcinogenicity" are not convincing (e.g., nickel monosulfide and lead oxide). Beryllium copper is presently before OSHA in another rulemaking and will not be discussed here. Thus, OSHA cannot accept on the merits Dr. Furst's conclusion that the carcinogenicity of each compound of a metal must be established independently. Nor does the position taken by Dr. Rogers, that "the question of carcinogenicity should be considered separately for each element, compound, mixture, alloy or other material. . . ." appear reasonable. To adopt this position would mean that regulation could be avoided and workers continued to be exposed to a carcinogenic material by a slight change in product composition. To take Dr. Rogers' position on mixtures literally would mean that data could not even be extrapolated from one batch of a commercial product to another. Moreover, limitation of resources would make this approach totally impractical, and uneconomical, even ignoring the years of exposure to workers that would pass before the results of testing of each batch were obtained.

Instead of adopting any extreme position, OSHA intends to use "structural similarity" of inorganic compounds in a judicious and appropriate manner, with careful exercise of scientific judgment. In individual rulemakings taken pursuant to this policy, it may be reasonable to associate the carcinogenic activity exhibited by one or more compounds of a metal with the metal itself or with one of its compounds formed *in vivo*. In such a case, inferences of potential hazard posed by other compounds would be justified, at least if the element were present in a biologically available form. In other cases, such as manganese, cited by Dr. Furst, the carcinogenic activity of one manganese compound may not necessarily justify an inference of hazard for other manganese compounds. It is important to treat each case on its merits, and to utilize the scientific information in an informed and careful manner in each rulemaking.

In summary, OSHA is persuaded by the testimony of expert witnesses that information on structural similarity should be used wherever it provides probative evidence of potential risks, subject to the exercise of expert scientific judgment, in the individual rulemakings taken pursuant to this policy and not foreclosed—one way or the other—by this rulemaking. OSHA is also persuaded by the testimony of Dr. Shubik, that failure to use structure-activity relationships in identifying and classifying potential carcinogens would be irresponsible. OSHA believes that the language in the final regulation is based upon a general scientific consensus and substantial evidence in the Record, *viz:*

§ 1990.111(c). "This Part applies to individual substances, groups of substances, or combinations or mixtures of substances which may be found in workplaces in the United States. In individual rulemaking proceedings under this Part, the identity and range of substances and mixtures to be covered by the standard will be specified and the appropriateness of applying the available evidence to the range of substances and mixtures proposed for regulation will be subject to scientific and policy review."

OSHA notes that this decision does not differ from the method by which OSHA has regulated potential occupational carcinogens in the past. For example, vinyl chloride, 29 CFR 1910.1017, was regulated without regard to other vinyl substances, trivalent and pentavalent arsenicals were regulated together as one substance, 29 CFR 1910.1018, and emissions from coke-oven operations were regulated as a process, 29 CFR 1910.1029. It is intended that this decision give OSHA and the public that needed scientific flexibility in regulating different or distinct potential carcinogenic substances in the workplace with maximum protection for the worker by regulatory decisions properly tailored to each regulated substance, combination of substances or process, whatever the case may be determined as appropriate in the individual rulemakings held pursuant to this policy.

VIII. The Attempt To Make Quantitative Estimates of Carcinogenic Risks for Regulatory Purposes From Test Animals

A. OSHA's Proposal

In the preamble to the proposed regulation (42 FR 54167), OSHA proposed tentatively to use quantitative estimates of carcinogenic risk, if at all, only at the point of "considering the

feasibility of the regulatory provisions of any given standard," but not for the purpose of "evaluating the expense and level of control considered feasible in view of the risk posed by any given substance." Citing papers by Mantel *et al.* (1975) and Mantel and Schneiderman (1975), the proposal pointed out the need to be cautious in estimating the nature of the dose-response relationship for any carcinogen. Citing a paper by Crump *et al.* (1976), OSHA referred to increasing evidence supporting the proposition that the response in terms of the number of individuals at risk within a population would be linear with dose, at least at low exposure levels:

"* * * linear dose-response relationships are likely to be approximately correct for many environmental carcinogens, and this should be publicly agreed for such substances, as it was for radiation 20 years ago." (Crump *et al.* 1976, p. 2979; Exhibit 6 to Hoel Statement.)

OSHA specifically invited the public's attention to the issue of whether quantitative estimates of risk should even be attempted for substances identified as potential occupational carcinogens and, if so, the methods to be employed for a quantitative estimation of (42 FR 54167).

B. General Response Received on the Issue

A very large response was received on this issue of quantitative estimation of risks. However, the opinions expressed varied widely, reflecting substantial disagreements about the relative merits, accuracy, and reliability of existing methods for risk estimation. Most participants agreed that the risks posed by potential carcinogens can be of widely differing magnitudes. Many participants also argued that some attempt should be made by OSHA to estimate risks as a function of exposure levels. However, there was great disagreement as to how these estimates should be used in regulatory procedures, if they are made at all. Some participants proposed that numerical estimates of risk should be used directly in cost/benefit balancing, where as other participants emphasized the uncertainties involved in low-dose risk estimation. Some participants believed that these uncertainties were so great that quantitative estimates should not be made at all.

OSHA believes that many of the comments did not fully take into account OSHA's statutory responsibility or the difficulties in extrapolating to low-dose human exposure. All the issues are discussed extensively below.

A number of the participants placed in the Record very useful summaries of scientific evidence on the feasibility of making estimates of risk at low doses, on the methods available for making such estimates, and on their reliability and limitations. Section XI.B contains a detailed discussion of the economic implications of regulatory procedures that rely on quantitative risk assessments. This section is restricted to the scientific evidence OSHA places particular weight on the testimony and exhibits offered by specialists in this field, and by scientists with responsibility for making and reviewing such estimates, either for regulatory agencies or as chair-persons of expert scientific committees. These witnesses included Dr. David Hoel (NIEHS), Mr. Richard Peto (Oxford Univ.), Dr. Marvin Schneiderman (NCI), Dr. David Rall (Director, NIEHS), Dr. Matthew Meselson (Harvard Univ.), Dr. Donald Kennedy (Commissioner, FDA), Dr. Adrian Gross (FDA), and Dr. Roy Albert (EPA). OSHA also places substantial weight on the comments of Dr. Richard Wilson (Harvard Univ.), who provided a detailed review of the issues and specific suggestions for procedures. In addition, OSHA places special weight on the reports of recent expert review committees, including the Safe Drinking Water Committee (NAS 1977), the Saccharin Study Committee (NAS 1978), and the Scientific Committee of the Food Safety Council (FSC 1978).

C. Review and Analysis of Comments

For the purpose of review and analysis, the comments and testimony received on this issue may be divided into several discrete groups:

1. General comments on the need to consider carcinogenic "potency" or to make quantitative estimates of risk.
2. Definitions of "potency" and its relation to low-dose risks.
3. Methods for extrapolating dose-response data to low doses.
4. Scaling factors for extrapolating from animals to man.
5. Factors complicating quantitative estimates.
6. Comments on the role of risk estimation in the regulatory process.
7. Specific proposals for making low-dose risk estimates and for using them in regulation.
8. Specific examples of risk calculations for individual chemicals.

1. General Comments on the Need To Consider Carcinogenic "Potency"

A number of participants suggested that rational regulation required the consideration of carcinogenic "potency". While this concept may be appealing, for many of the proposals the term was not properly defined, nor were detailed regulatory frameworks utilizing the potency concept outlined. For example, both API and AIHC recommended the use of quantitative risk estimates in non-specific terms, as follows:

"The amounts of different chemicals known to have non-carcinogenic toxic effects can vary by several orders of magnitude [46]; a different permissible exposure limit for each is therefore appropriate and justified. Since it has been demonstrated that the amounts of different substances that produce carcinogenic effects can likewise differ by a million fold or more [49], it seems irrational for the OSHA proposal to proceed on the basis that all known and potential carcinogens pose equivalent risks (by requiring the "lowest feasible" permissible exposure level in all cases). Carcinogens, like noncarcinogen toxins, should be classified or ranked in terms of potency, and regulated according to the degree of hazard that their use or uses presents to employees. For example, bischloromethylether is a very potent known human carcinogen; vinyl chloride is much less potent. More severe controls clearly are warranted for the former. Greater priority should be accorded to regulating a substance that is a potent carcinogen than a substance that is a weak carcinogen, where the extent of employee exposure is the same.

"The AIHC alternative calls for categorizing both human and animal carcinogens in terms of the potency of carcinogenic response, "high," "intermediate," or "low". These classifications are provided primarily to assist in establishing regulatory priorities. (However, a low potency carcinogen may warrant high priority if exposures are high and extensive.) The potency distinctions also would be an indicator of the regulatory controls to be imposed: more stringent controls for the more potent carcinogens. However, the categories would not inflexibly determine the regulatory controls. Such controls, including the means of achieving the permissible exposure level, would be determined on a case-by-case basis in light of assessments of risks and benefits. Controls and exposure levels could easily differ for two substances in the same category, depending on the circumstances of each case." (AIHC Alternative Proposal, pp. 30–31)

* * * * *

"It is possible to determine through statistical techniques alone that considerable differences exist in the potency of suspect carcinogens. For example, exposure to certain chemicals has resulted in the development of cancers only at very high concentrations and/or after lengthy periods of exposure, and then at levels only marginally more significant than for the control group. Yet, other substances have generated substantial increases in the incidence of neoplasms even after brief or low level exposures. Thus, for example, the environmental pollutant aflatoxin requires less than one microgram to induce liver tumors in rodents, and saccharin was tested at 7.5% in the diet." Furst Statement 21

"OSHA's current proposal does not take even obvious differences in potency into account. There are two reasons why OSHA should consider such information. First, such

information is necessary to prioritize substances for regulatory control: the most pressing health dangers should be controlled first. Second, without such information, OSHA will be unable to determine what level of health protection is feasible." (API, S. 54–55)

AIHC also proposed that OSHA should include assessments of risk in procedures for setting priorities:

"Assessment of risk in this context means: (i) evaluation of the data to determine whether the quality of the epidemiological study or animal test provides a valid data base for a determination that a human cancer risk is presented by exposure to the substance; and (ii) evaluation of the potency of the substance with respect to human risk. This latter function includes selection of appropriate extrapolation techniques and consideration of the relevant metabolic and pharmacokinetic data as available." (AIHC Memorandum on Priorities, p. 3)

A number of individual witnesses also made comments to the same general effect. For example, Dr. Francis J. C. Roe (AIHC) made the following general conclusion:

"(vii) Carcinogens differ in intrinsic potency and this should be taken into account in predicting possible human hazard." (Roe, S. 76)

Dr. Richard Wilson (Harvard Univ.), introducing his statement with detailed proposals for risk estimation, summarized his recommendations as follows:

"I believe it is possible to make an adequate risk analysis from data on carcinogenesis in animals, and particularly in rodents. The evidence suggests that chemicals vary in their potency by factors of 100,000, and that potency in any species can be factored very roughly into an in-human potency multiplied by a species factor, recognizing that chemical insults may strike different organs in different species.

* * * * *

"I have done some of this and I believe it is possible to calculate then the carcinogenic risk to man for any chemical where there is animal data. I have summarized some comparisons, and Professor Meselson has done also." (Wilson, Tr. 3364–3365)

Later, Dr. Wilson concluded:

"So therefore, I think the whole purpose of the OSHA proposal would be enhanced if one defined the 'as low as feasible' for exposures in terms of a calculation of risk and made some estimate of how much one could afford to pay to reduce that risk." (Wilson, Tr. 3372)

Dr. A. E. M. McLean (AIHC) commented as follows:

"OSHA ignores the concept of varying potency in carcinogens and proposes to treat all substances meeting its overly-broad Category I criteria alike, requiring the same regulatory response for each. This concept does not accord with reality, common sense or good science." (McLean, S. 5)

The Reserve Mining Co. commented as follows:

"It is undisputed that carcinogens vary in potency. As noted in the 'Supplementary Information":

"In comparable test systems, chemical carcinogens can vary in the responses they elicit by as much as a factor of 10^7 (10,000,000) (WHO Tech. Rept. 546, p..11)" (42 FR 54165). While recognizing that the potencies of carcinogens can vary by a factor of ten million, the OSHA proposal would gloss over such obvious distinctions and generically treat all carcinogens as one, subject to the same compliance standard. Such a generalized or generic approach to the regulation of carcinogens is at odds with recent scientific thought." (Reserve Mining, S. 11–12)

Dr. Robert Eckardt (American Occupational Medicine Assoc.) made the following statement:

"That there are differences in potency between carcinogens is a well-established fact. This is illustrated in accompanying Table 1 from the literature or from government study reports. It is evident from this table that the effective dose for various cancer-producing agents in animals (that is, their potency) ranges from over 1% in the diet to as little as a few micrograms per day. Further, as stated recently by Boyland (J. Soc. Occup. Med. 27: 98, 1977), 'Thus there is a million-fold variation in the activity of carcinogenic substances when expressed on the basis of dose required'." (Eckardt, S. 2–3)

Dr. Robert A. Scala (Exxon) expressed a similar viewpoint, although he defined "potency" in a totally different way:

"The individual dose-response curve, in comparison with other dose-response curves of chemicals, indicate differences in potency. For an individual chemical determined by animal testing to be a carcinogen, the potency (i.e. tumor-yield, *or* time-to-tumor, *or* total percentage of animals affected, *or* numbers of tumors per animal) can be related to dose rate and total dose administered. These factors differ widely for different compounds. Any classification system which simply ranks materials as carcinogenic or noncarcinogenic and fails to differentiate among them on the basis of potency, would not reflect the potential carcinogenic risk differences represented by different chemical compounds. To be useful, a system for classifying chemicals which present a potential chemical risk must differentiate between high, medium, and low potency carcinogens. Otherwise, the primary purpose of assessing the risk represented by a particular carcinogen will not be achieved. It would be pointless to group an extremely weak carcinogen with an extremely potent carcinogen, since both the priority for action and the specific regulatory response should be markedly different for them." (Scala, S. 10–11)

Dr. Authur Furst (Univ. of San Francisco) made a similar recommendation:

"1. OSHA should ask the National Academy of Sciences, or some other body with broad-based expertise in dealing with carcinogens and cancer, to appoint a Committee to establish criteria for characterizing the carcinogenic potential of chemical substances. These criteria should go beyond the simple determination of whether or not a substance is a "carcinogen" to indicate whether or not there is actual evidence of a carcinogenic potential in humans, thus differentiating between human carcinogens and demonstrated animal carcinogens, and should also indicate the relative potency of both human carcinogens and animal carcinogens." (Furst, S. 29)

Dr. Paul Kotin (Johns-Manville) listed as one of the "crucial deficiencies" in the OSHA proposal:

"The grouping of all carcinogens into a single category for regulation, in the face of universally recognized differences in potency, mode of action, and species response." (Kotin, S. 29)

To meet this perceived deficiency, he made the following recommendations:

"3. The validity of risk level assessment must be substituted for the rigidity of the "lowest feasible level" philosophy.

4. The results of the study of risk assessment must be applied to a risk/benefit analysis." (Kotin, S. 32)

Dr. Richard Zeckhauser (Harvard Univ.) made the following statement:

". . . the classification system totally ignores evidence of the potency of potential carcinogens. Two, it ignores many important aspects of dose-response relationships . . . and this is related to the potency." At the very least, some rough distinctions should be made on the basis of potency. Surely a substance shown to be carcinogenic to humans at exposures approaching current occupational levels ought to be treated differently than one for which the evidence is restricted to very high doses administered to animals by a route other than those encountered in the workplace." " (Tr. 4317–4318, quoting from his own draft of an unpublished paper)

Dr. Philippe Shubik (Eppley Institute, Univ. of Nebraska) commented as follows:

"The failure to appreciate the fact that carcinogens may differ in their potency by up to seven orders of magnitude considerably reduces the effectiveness of these proposals in the control of occupational carcinogens. Some attempt to divide carcinogens into strong and weak actors is essential." (Shubik, S. 33–34)

A number of other witnesses made similar comments and proposals.

In addition to these recommendations that "potency" and/or risk estimation be used in some manner to regulate carcinogens, a second group of participants testified that quantitative estimates of carcinogenic risks can and should be made—but only if their

uncertainties are explicitly recognized and their use carefully limited. These witnesses felt that risk assessments, given the uncertainties involved, would play a more useful role in the structuring of priorities than in the standard-setting process. Dr. Donald Kennedy (Commissioner, FDA) made the following comments:

"I believe it important to note that not all carcinogens are equally potent and that there are vast differences in the levels of human exposure to carcinogens. Quantification of carcinogenic risks, regardless of the method used, takes into account these differences and permits the identification of the most important hazards, the least important or insignificant, and those falling between these limits. I urge OSHA to use quantification of risk as one component of decision-making. I have no suggestion about the best way to quantify risk, but it is clear to me that, from a scientific view, it is important to do so." (Kennedy, S. 11–12)

Dr. David Hoel (NIEHS), a specialist in quantitative risk assessment, introduced his direct testimony as follows:

"The need for a quantitative approach to human risk assessment can be based upon two premises: (1) Some carcinogens or their active metabolites directly interact with cellular DNA and produce a form of cancer which is the result of a single cell somatic mutation (see Cairns (1975)). Thus we are at least theoretically in a no-threshold situation for some chemicals and therefore absolute safety cannot be assured (see NAS/NRC (1977)). (2) Quantitatively there is a broad range of carcinogenic potencies among chemical carcinogens (see NAS/NRC (1977), Meselson and Russell (1977)).

"Given these two concepts there clearly is a need to assess quantitatively the risk to man at low exposure levels in order to have a rational standard setting and methodology." (Hoel, S. 1–2)

Dr. David Rall (Director, NIEHS) stated that the concept of "feasibility" includes consideration of the magnitude of carcinogenic risks, and that scientists should both estimate such risks and define the uncertainties in such estimates:

"Ultimately, however, the selection of a "feasible" level depends on a judgment as to when the costs of control (which may include health risks and resource costs as well as economic costs) are justified by the magnitude of the carcinogenic risks posed by unregulated exposure . . . The task of the environmental health scientist is to estimate as precisely as possible the magnitude of the risks posed by exposure, and to define the uncertainties involved in these estimates. The scientist should also specify the point at which scientific analysis ends and social judgment must be involved." (Rall, S. 1–2)

Mr. Richard Peto (Oxford Univ.) agreed that the selection of a "feasible" level of control included some consideration of the magnitude of potential risks. (Peto, Tr. 2554)

Mr. Steven Jellinek and Dr. Roy Albert (EPA) described how quantitative risk assessment is used by the Environmental Protection Agency:

"EPA uses a two-step decision-making process to regulate potential carcinogens. The first decision faced is whether a particular substance poses a cancer risk. The second decision is what regulatory action, if any, should be taken to reduce the risk. The two decisions are reached separately.

"Once EPA has determined that a substance being evaluated does pose a carcinogenic risk, EPA proceeds to independent analyses of the magnitude of the risk posed by the substance and, where the law permits us to do so, the socio-economic impacts of regulating the substance. Both analyses are completed before the Agency reaches a regulatory decision. The magnitude of the risk plays a significant role in EPA's regulatory process, entering into the decision whether to regulate a substance, what priority we give to regulation of the substance, and what type of regulatory action (if any) we should take." (Jellinek, S, 2)

"The second question of how much cancer the agent is likely to cause is answered by use of various mathematical extrapolation models applied to the animal or epidemiological results together with estimates of the levels of exposure to the agent to the extent that such estimates can be made. These quantitative estimates are regarded as crude and offered only to give rough estimates of the magnitude of the public health problem. Such estimates may be of use in setting regulatory priorities or in determining levels of feasible control." (Albert, S. 2)

Mr. Jellinek suggested that OSHA should use quantitative estimates of risk for two purposes:

"Second, we encourage OSHA to include risk estimation in its regulatory process. While cancer risk estimation is an imprecise endeavor involving many uncertainties, such estimation does succeed in providing some measure of the magnitude of risk posed by a substance. Such estimation should be used, in some instances, to determine whether to regulate. If a substance is believed to be a carcinogen but is a weak carcinogen to which few persons are exposed, the best regulatory course might be to defer any regulation in favor of concentrating limited resources on higher toxicity, higher exposure substances. OSHA's proposal does not appear to permit the agency to adopt this course. We believe that OSHA also should use estimation of risk to help establish priorities and to help determine "feasibility" of various levels of control. The greater the degree of risk posed by a substance, the tighter the control should be of that substance." (Jellinek, S. 5–6)

Dr. Albert also recommended that OSHA should use quantitative risk assessment for the same two specific purposes:

"Finally, a comment on the matter of quantitation of cancer risks. The extrapolation of cancer risks to very low levels of exposure is undoubtedly more useful to EPA than OSHA. In the general environment, exposures to carcinogens can commonly be very low and involve large populations. In the occupational setting the potential for exposure in always high. Nevertheless, because carcinogens can vary in potency by as much as a million fold, OSHA should strongly consider using quantitiative risk assessment to the extent possible for prioritization of chemicals and as a factor in judging feasibility of regulatory control." (Albert, S. 6)

Dr. Joyce McCann (Univ. of Calif.) made the following suggestions in the summary of her statement:

"II. Quantitative human risk extrapolations from animal carcinogencity tests can be useful within the lowest feasible level framework proposed by OSHA.

A. There may be examples where "feasibility" and acceptable risk are quite incompatible.

B. Risk estimates can be wrong by an order of magnitude, or even more, and still be useful as rough estimates in determining if the lowest feasible level is compatible with acceptable risk.

C. Although the data are not extensive, they indicate that carcinogenic potencies of chemicals in rodents and in humans are roughly similar.

D. For use in low dose extrapolations, a linear dose response, even though uncertain, is the most reasonable assumption consistent with the use of risk assessment calculations for the purpose of determining upper limit estimates.

E. Although risk estimates can be useful within the context of the lowest feasible level approach, they should not be used to set exposure levels higher than the lowest levels feasible." (McCann, S. 3–4)

These and other witnesses stressed the uncertainties inherent in quantitative risk estimates, and proposed their use only for limited purposes, as discussed more fully below.

In contrast, a third group of witnesses expressed the opinion that quantitative risk estimates could not and should not be made at all, at least in circumstances where experimental data in animals were the only basis for estimating risks to exposed humans. Dr. Richard Griesemer (NCI) expressed this opinion as follows:

"And where [the general principles of toxicology] do not apply, in my opinion, is when one tries to extrapolate to lower dose levels. In my opinion, as I have said, I do not believe that can be done, even for the animal." (Griesemer, Tr. 936)

He continued:

"But my belief then is that we should not attempt to extrapolate dose data or route data from animals to man; I do not think it is possible." (Griesemer, Tr. 957)

Dr. William Lijinsky (NCI–FCRC) made the following statements:

"With only a single exception until now, all of the known agents carcinogenic in man have reproduced this carcinogenic effect in one or more species of experimental animals. But without reliable indication, man is more or less susceptible to their carcinogenic action than are the animals. This makes risk extrapolation impossible with our present knowledge other than to state a carcinogenic risk exists." (Lijinsky, Tr. 1018)

He added:

"I do not extrapolate risk. I do not think it is possible. As I said in my summary, I do not think it is possible to extrapolate risk at all at the moment, except to say that any compound which induces tumors in experimental animals in a well-conducted test poses a risk to man if man is exposed to it. That is all you can say. You cannot measure the risk."

* * * * *

"I said that there might be strong and weak carcinogens. I did not say we could identify which they were. I implied that there might be strong and weak carcinogens, but I did not say that we could identify them, or we could tell them one from the other in any way." (Lijinsky, Tr. 1056)

Similar statements were made by other distinguished scientists: Dr. Umberto Saffiotti (NCI), Tr. 1009; Dr. Benjamin Trump (Univ. of Md.), Tr. 2019; Dr. Curtis Harris (NCI), Tr. 2019; Dr. Isadore Dubin (Medical College of Penn.), Tr. 1128, 1151, 1166, 1199, 1202; and Dr. Bernard Weinstein (Columbia Univ.), Tr. 2284. Dr. Curtis Harris (NCI) was explicit in stating that we do not have test systems which can be used to predict "potency" of chemicals in humans:

"Beta-naphthylamine is a good example. That is why I think we have to be very hesitant in making quantitative extrapolations. I do not think we can do that. Beta-naphthylamine for workers who have been exposed to that compound for over a five-year period causes 100 percent bladder cancer. Now, you would have never predicted that from the animal tests. You would have predicted that it is a carcinogen, but you would not have predicted its potency. And that is very unfortunate. I wish we had test systems in which we could predict potency, but we do not." (Harris, Tr. 1974–1975)

Dr. Griesemer (NCI) made a similar comment:

"Intellectually and intuitively, I believe that it is very likely that there is a difference in potency of chemicals. When it comes to absolute evidence that demonstrates potency, I cannot do it, because of the confounding factors in the experiments." (Griesemer, Tr. 1005).

Three recent reports of committees of the National Academy of Sciences have given similarly conflicting recommendations on the use of quantitative risk assessment. Dr. David Rall (Director, NIEHS) introduced the section of the report of The Safe Drinking Water Committee which dealt with safety and risk assessment (NAS 1977a). This chapter was written by a subcommittee of which Dr. Rall was chairman. One of the four principles enunciated by the subcommittee as underlying efforts to assess the irreversible effects of long-continued exposure to carcinogenic substances at low dose rates was the following:

"Principle 4:

"Materials should be assessed in terms of human risk, rather than as "safe" or "unsafe."

"The limitations of the current experimental techniques do not allow us to establish safe doses, but with the help of statistical methods we may be able to estimate an upper limit of the risk to human populations. To calculate such a risk, we need data to estimate population exposure; a valid, accurate, precise, and reproducible assay procedure in animals; and appropriate statistical methods. Several general guidelines may be presented. First, no rigid, generally applicable procedure can be recommended for testing all toxic agents. Substances differ too much in their overall effects, and the design of appropriate assays will ultimately have to be left to the well-informed judgment of expert investigators. If substances that affect large populations are found to be carcinogenic, experiments of much wider scope may have to be conducted to obtain more detailed information on their possible effects in humans." (NAS, 1977a, p. 56; Appendix I to Rall Statement)

Elsewhere in the chapter the subcommittee discussed methods for low-dose extrapolation and actually calculated potential risks for exposure to certain substances in drinking water (*ibid.*, p. 794). However, as discussed below, the subcommittee strongly emphasized the uncertainties in low-dose risk extrapolation, and the committee did not use their risk estimates to propose drinking water standards.

The Pesticide Information Review and Evaluation Committee (NAS, 1977b) considered it impossible to make quantitative estimates of risk to humans:

"In conclusion, chemical carcinogens appear to act in laboratory animals and humans via similar and possibly identical pathways. One must assume, therefore, that chemicals which are carcinogenic in animals may be carcinogenic in humans, but the committee is unwilling to quantify this risk. The existence of large species differences in responses to chemical carcinogens is a fundamental uncertainty in the extrapolation of carcinogenicity data from laboratory animals to humans.

"Through the use of data generated from experiments with animals, it is possible to attempt estimation of the risk to humans associated with exposure to chlordane, heptachlor, and/or their metabolites. Unfortunately, any such assessment must rely to a large degree on subjective judgment about the magnitude of certain important numerical quantities because of the lack of specific knowledge about the nature of the dose-response curves for the tested animal species beyond the fixed experimental range (i.e., within the range normally encountered in the environment). Furthermore, assumptions must also be made about the unknown effects of potential species differences with respect to physiological, metabolic, and/or carcinogenic processes involved. Clearly this assessment process is not entirely objective. Since the committee was charged with answering questions based on scientific facts, it considers it inappropriate to adopt such a judgmental procedure." (NAS, 1977b, p. 29; Exhibit 10d to Epstein Statement)

Most recently the Report of the Committee for a Study on Saccharin and Food Safety Policy (NAS 1978) discussed this issue at some length. After presenting a set of disparate estimates of potential human risks, the Committee concluded:

Since animal studies that are properly conducted to detect carcinogenic activity are qualitatively predictive of human responses, the committee concludes that saccharin ingestion presents a predicted cancer risk to humans. However, because of the substantial uncertainties in extrapolations from experimental doses to human exposure levels, the committee concludes that quantitation of risks to humans cannot be made with confidence. (Table 3–8). (NAS, 1978, p. 3–74, emphasis in original).

Finally, the Food Safety Council recently issued a report which recommended quantitative assessment of risks for all food components and calculated "virtually safe doses" for a number of carcinogens:

"When toxic or other undesirable effects are found in test procedures, it is almost always at exaggerated dose levels. It then becomes necessary to estimate the probability of such a response at dose levels encountered under normal conditions of consumption. A procedure for making such an estimate is presented in the section entitled, Quantitative Risk Assessment." (Food Safety Council, 1978, p. 4; Hearing Exhibit 227)

In summary, there is considerable divergence of opinion among scientists on the issue of quantitative risk assessments. Although many participants believed it desirable to differentiate between carcinogens on the basis of the magnitude of the risks they pose, most recognized that there is considerable uncertainty in estimates of these risks, and a substantial number of distinguished participants believe that such estimates cannot be made at all. (See subsections 7 and 8 below.)

2. Definitions of "Potency" and Its Relationship to Low-Dose Risks

Many participants to this rulemaking used the term "potency" in imprecise

ways. In the passages quoted above, Dr. Eckardt used the term as equivalent to "effective dose" (concentration in diet or daily dose in mg/kg) whereas Dr. Scala used it as equivalent to effect ("tumor-yield, or time-to-tumor, or total percentage of animals affected, or numbers of tumors per animal"). Dr. Zeckhauser originally defined potency as:

"basically how strong the carcinogenic *potential* of the substance is" (Tr. 4335, emphasis added).

However, he subsequently gave two different definitions:

"As I understood potency, it is—I think one interpretation that is sometimes given to it is *the slope of the dose-response curve,* which basically says how much of a particular reaction you get for an increase in the dose level. So this would—potency, to give you a more general interpretation, as I interpreted it, means two substances to which we are exposed at the same level; the more potent one will cause more of whatever phenomenon we happen to be looking at. If it is carcinogenesis, the more potent substance, and *if I say Substance A is twice as potent as Substance B, then I would say that over the relevant range that if I exposed 10,000 workers to each of these two substances at the same levels of concentration, there would be twice as many workers contracting cancer in one sample as in the other, on an expected value basis.*

* * * * *

"And what it means is it is an abstract concept which can be applied in a great variety of areas which *relates exposure to consequence.* And therefore, it applies as well to human beings as it does to animals. We may not have the information on human beings, but certainly the potency concept applies to human beings." (Tr. 4369–4370, emphasis added)

Dr. Paul Kotin (Johns-Manville) defined potency as:

"The ability to induce neoplasms on the basis of the concentration of the agent multiplied by its time, which is the pharmacologic definition of dose . . ." (Kotin, Tr. 8683).

Dr. Kotin also drew an analogy between the term potency in chemical carcinogenesis and the term "linear energy transfer" in radiation carcinogenesis (Kotin, Tr. 4886). Although the latter is a measure of the effects of radiation at the cellular level, Dr. Kotin stated that he was equating this with carcinogenic potency at the whole-animal level (Kotin, Tr. 8701–8703).

Only two scientifically precise definitions of potency were presented in the record. Dr. Joyce McCann (Univ. of Calif.) and Dr. Matthew Meselson (Harvard Univ.) designated the term potency as the daily dose in mg/kg giving 50% tumor induction in 24 months in a rodent bioassay. Dr. Lamm (API Alternatives Panel) gave a similar definition. The term was precisely defined in a paper by Meselson and Russell (1977), who also gave an operational method for calculating it from bioassay data:

"We define the carcinogenic potency, k, as $1n2/D_{\frac{1}{2}}$, where $D_{\frac{1}{2}}$ is the daily animal dose which gives 50% cumulative single-risk incidence of induced cancer after 2 years of exposure, a time chosen to approximate the normal average life-span of laboratory rats, mice, and hamsters.

* * * * *

"Animal experiments generally do not provide k directly. We obtain it in two steps. First, we estimate the cumulative single-risk incidence of tumor, I, at a time t measured from the start of treatment at dose rate D. Then we use the relationship $k = [-\ln(1-I)/(Dt^{n+1})]$, where time is expressed in units of 2 years. This serves to normalize experimental data to an accumulated single-risk incidence of 50% and an exposure time of 2 years. The relationship follows from the definition of k and the assumption that the proportion of previously unaffected animals developing tumors per unit time after exposure for a time t varies with the first power of D and the nth power of t. For continuous carcinogenesis, this dose and time dependence, with $2<n<4$, provides an approximation to the data for a variety of animal and human cancers (Druckrey 1967; Doll 1971). Since there is not adequate information available to determine the best value of n for most of the compounds of interest here, we selected the value $n=3$ at the outset and have used it throughout. In any case, the rejection of experiments with exposure times of less than 50 weeks helps to avoid very large errors in normalization." (Meselson and Russell, 1977, p. 1474; Exhibit 17 to Hoel Statement)

Dr. Richard Wilson (Harvard Univ.) introduced and defined the term as follows:

"This risk contains two factors; the exposure to the carcinogen, and the carcinogenic effect at this exposure. This will be a simple product *if* it is assumed that the dose-response relationship is linear. The *slope* of this dose-response relationship is the *potency* and we obtain a simple relationship at low doses." (Wilson, S. 11)

* * * * *

"The relationship between fractional cancer incidence and exposure (E) (=dose rate) is $I=(1-\exp(-PE))=PE$ at low exposure where P is a constant called the potency. Sometimes the fractional cancer incidence is called the cancer risk.

"This definition of potency assumes a proportional response even if animals show toxic effects. For the moment, I will ignore details such as these, and bring them in as corrections later." (Wilson, 1978, p. 8; Hearing Exhibit 51)

For an operational definition of potency, Dr. Wilson (Harvard Univ.) specified that one should take response data at high doses, draw a straight line to the origin, and calculate the potency as the slope of this line (Tr. 3428–3429). As is made clear in these quoted statements, Dr. Wilson's definition of potency is dependent on the assumption of a linear dose-response relationship. Under this assumption, his definition is essentially the same as that of Meselson and Russell (Tr. 3428). However, if the dose-response relationship is not linear, the two definitions are not necessarily related at all. For example, if two carcinogens have dose-response curves of different shapes, one may be relatively more "potent" at high doses and the other relatively more "potent" at low doses. Thus, unless a specific mathematical form for the dose-response relationship can be assumed, there is no unique definition of "potency" that is applicable to any carcinogen unless a specific region of the dose-response relationship is specified (as was done, for example, by Meselson and Russell).

OSHA's primary concern is with risks to workers exposed at low doses, and for this purpose measurements of responses at high doses are not directly applicable unless some method of extrapolation can be agreed upon. However, all the definitions of potency proffered at the hearing (including Wilson's—Tr. 3429) are of very limited relevance since they are based on measurements of responses at high doses. The important question at issue is a different one: how to estimate risks at low exposure levels.

Another fundamental consideration is that "potency" is not an intrinsic property of a carcinogen, but can only be defined in terms of a specific test system. Dr. Peter Goldman (API) stated this most explicitly:

"Well, I think that first of all, potency has to be defined in terms of a particular test system.

"In other words, the measurement that is made is critical and the system in which that measurement is made. And then just, if we now in that system have two compounds A and B and we find that we get the same response in these two systems with twice as much A as B, then we can say that A is half as potent as B.

"In other words, and there are a little technical tricks one looks for 50% response and equates compounds on the basis of weight required to give the 50% response. But basically, I think that that is the definition of potency.

"And, I might point out that perhaps some confusion arises in that in certain test systems compound A can be more potent than compound B, whereas in another test system the reverse can occur." (Goldman, Tr. 4469)

Dr. Umberto Saffiotti (NCI) also discussed this issue at some length:

"There has been discussion of the word "potency" as if that were something we can identify as being intrinsic in the molecular structure of a chemical; a chemical carries that potency. Now, potency obviously is potency as measured by an effect. The effect is in interaction of the agent with a host, and the potency that we can—the effects that we measure and can try and classify in potency, are the results of that chemical biological interaction. Therefore, they are dependent on the biological conditions under which the interaction occurs.

"Now, if we change that, we are to be—we are expecting that the total effect will change. Therefore, we are measuring something that is a variable by itself. Now, if that range of variables were narrow and if we could say by and large, if something has a potency that we can measure by the intensity of this effect and the effect in another species or system or under other conditions may vary from it, but probably not more than by a factor of two, we would then have a least a certain basis for correlation if we were comparing minor variations there with possibly large variations between different chemicals.

"Now, so far we have been looking into this matter with a great deal of interest because it would be very useful scientifically to be able to make some sense out of the whole issue of potency. I hope some day we will find some new approach to it that would allow us to do it. At the present time we find such a marked variation in the response, both at the inter-individual level, particularly as it applies to people, and at the species-to-species or biological system to biological system level, that we cannot really extrapolate the magnitude of an effect as measured in one case to the prediction of an effect in another. Therefore, the term "potency," which is implying a continuum, a property, is to me really not possible to document in a scientifically acceptable way. We can have different orders of effect within a biological system, then when we change the system we change the effect." (Saffiotti, Tr. 1005–1007)

OSHA concludes that much of the testimony addressed to carcinogenic "potency" was either confused or relevant only to responses at high doses. Since standards setting is concerned with estimation at low doses, such concepts are not directly relevant. The remainder of this discussion will be limited to analysis of testimony on the subject of estimation of risks resulting from low doses.

3. *Methods of extrapolating dose-response data to low dose levels*

Extrapolation of dose-response data to predict potential risks at low doses requires some kind of assumption about the mathematical form of the dose-response relationship. Several detailed descriptions of mathematical models incorporating such assumptions are available. One of the simplest introductions is provided in the report of the Committee for a Study of Saccharin and Food Safety Policy (NAS 1978):

"A chemical that has been associated with an increased cancer incidence in bioassays of laboratory animals is likely to be a carcinogen in humans. Extrapolation to humans of cancer incidence in animals is necessary to quantify the expected degree of risk for humans that are exposed to concentrations of the chemical that differ from those in bioassays of animals. This extrapolation procedure consists of two basic steps:

1. within the test animal species, extrapolation of the experimental results of tests performed at high exposure or dose levels to much lower exposures in animals, which correspond to human exposures; and

2. extrapolation of these estimated risks for animals at low doses to the risks for humans at comparable levels.

"The first step in this process requires the assumption of some biological model, which implies a mathematical rule that relates the dose level of a particular carcinogen to an observable response, e.g., the occurrence of a particular type of tumor at any time within the animal's natural lifespan or lifetime for the duration of the study. This assumption is normally required since the animal studies are conducted at much higher exposure levels than are commonly found for human exposures. These high exposure levels must be used to obtain measurable results with a limited number of animals. At dose levels that correspond to common human exposures, several thousand animals would be needed to estimate the increased carcinogenic risk in humans.

"Many theoretical dose-response models of carcinogenesis have been proposed, each of which leads to a particular mathematical form for this dose-response relationship. All theories have one concept in common: that there is no known uniform threshold dose below which any carcinogenic response is impossible for all individuals at risk. Even if thresholds do actually exist, it is scientifically impossible to measure them or to prove their existence. In addition, the assumption of one uniform threshold for heterogenous groups is unrealistic. It is much more likely that each member of the population has an individual threshold level which is some complex function of unique biochemical and physiological composition. A further argument against use of threshold models for the estimation of attributable risk is that the environment contains many carcinogenic agents and that the particular chemical in question may be acting additively over and above this "background." Therefore, since tumors do appear spontaneously in a central population, the threshold, assuming it does exist, has probably already been exceeded by the environmental background. Craig and Miller (1974), in a review of 151 dose-response curves, found only one to be inconsistent with the no-threshold hypothesis.

"Some of the more commonly used mathematical extrapolation modes are the following:

"The *probit model* is derived from the assumption that each member of the population has his own tolerance level for the chemical, below which there will be no response and above which the subject will respond. These tolerances are further assumed to vary among members of the population and to follow a log-normal probability distribution. Mantel and Bryan (1961) have suggested use of a modification of this model for extrapolation of carcinogenesis bioassays from high to low doses. Since the tolerance distribution for the homogeneous laboratory animal population should have a smaller variation than that of the heterogeneous human population, they suggest that the risk extrapolation be based on a model with a more shallow slope than that observed in the bioassay. This shallow slope should be no greater than the average true slope over the extrapolation range. A slope of one probit per 10-fold change in dose is commonly used for this Mantel-Bryan extrapolation.

"The *single-hit, or single-event, model* is derived from the assumption that cancer starts in a single cell as the result of some random event, or "hit", which produces an irreversible change in the cell's DNA. It is further assumed that the probability of this event, attributable to the carcinogen in question, is proportional to the exposure level.

"The *multi-stage model* (Crump *et al.*, 1976), a generalization of this single-event model, is derived by assuming that the carcinogenic process consists of some unknown number of stages that are required for cancer expression. The probability of at least one of the transitions from one stage to another is assumed to be a property of the particular carcinogen in the same manner as the single-event model.

"Other models, such as the log-logistic and multi-hit models (Food Safety Council, 1978) have also been proposed, but the three models described above produce a range of extrapolations that would be obtained by most other models. Models of dose-response based on the actions and reactions on *in-vivo* chemical and physiologic processes have also been proposed (Gehring and Blau, 1977). These are determined by a series of differential equations corresponding to multicompartmental models of the chemical processes within the body that correspond to the internal fate of the chemical carcinogen.

"The difficulty with using any of these dose-response models for high- to low-dose extrapolation purposes is their similarity over the observable response range, 5% to 95% response rates, contrasted with their dissimilarity in the range of very low response rates (Table 3–7).

Although all three models are similar in the observation range, the lower part of the table shows that extrapolation to exposure levels that are expected to give very low response rates is highly dependent upon the choice of mathematical model. The upper part of Table 3–7 shows that three of the most commonly used models differ by very little over a 256-fold dose range. At a dose that is 1/1000 of the 50% response dose, the single-hit model gives an estimated response rate that is 200 times as large as the log-normal model. The fact that a limited animal bioassay that is conducted at dose levels high enough to give observable response rates cannot discriminate among these various models and the fact that these same models are

substantially divergent at lower dose levels provides the major uncertainty for high- to low-dose extrapolation. (NAS 1978, pp. 3–61—3–66).

TABLE 3–7.—Expected Response Rates as a Function of Dose for Different Dose-Response Models*

Relative Dose	Percent		
	Log Normal	Log Logistic	Single Hit
16	98	98	99+
8	93	92	99
4	84	84	94
2	69	70	75
1	50	50	50
.50	31	30	39
.25	16	15	16
.125	7	8	8
.063	2	4	4
0.01	.05	.4	.7
0.001	.00035	.026	.07
0.0001	.0000001	.0016	.007

* Data from USDHEW 1971.

A number of other sources provide more technical accounts of the mathematical models available. Dr. David Hoel (NIEHS) provided the following introduction to the multi-stage model and showed its relationship to the linear model:

"Several quantitative theories of carcinogenesis have been proposed which relate tumor incidence with both dose rate and duration of exposure of the carcinogen. These models generally assume that the carcinogenesis process is single cell in origin and is the result of several stages which can include somatic mutation. The transitional events are individually assumed to depend linearly on dose rate. This then leads in general to a model in which the probability of tumor is approximately a low order polynomial in dose rate. In the low dose region which would relate to environmental levels one finds that the response is well approximated by a lidear function of dse rate (Armtage ad Doll, 1961; Crump *et al.*, 1976). Another class of dose response models which have been applied are those which have a history in bioassay work. For example, both the logistic and probit functions are used for estimating LD_{50} in toxicology. Mantel and Bryan (1961) have applied the probit to low dose estimation in carcinogenesis. Its drawback is primarily that the model is not based upon a mathematical description of a biological mechanism as is the case with the multistage somatic mutation model. Since it produces quite different results in the low dose region it probably should not be applied in those cases where it is believed that the carcinogen is direct acting with cellular DNA as is proposed in the multistage models (Crump *et al.*, 1976; Guess *et al.*, 1977).

"Of the multistage models the one discussed by Armitage and Doll (1961) has received considerable attention (Crump *et al.*, 1976 and 1977; Guess and Crump, 1976; Guess *et al.*, 1977; Hartley and Sielkin, 1977). The function which is used states that the probability of a tumor by time t using dose rate d is

$$P(d,t)=1-\exp[-g(d)h(t)]$$

where

$$g(d)=\prod_{i=1}^{k}(\alpha_i+\beta_i d)$$

with $\alpha_i>0, \beta_i>0$ for i=1, . . ., k. This represents a k stage or mutational step model with dosage and time factoring. The above mentioned authors have developed maximum likelihood estimates for the unknown parameters in the model. Further they have approximate confidence estimates on low dose estimates of the probability of tumor. These procedures are mathematically complicated in that computing algorithms are required in order-to obtain the estimates. Recently Guess *et al.* (1977) have applied these algorithms to experimental carcinogenesis data on vinyl chloride, DDT, chloroform, DMN and dieldrin. In all of these cases k=1 or 2 was found to provide the best fit although DMN yielded a zero estimate of the linear coefficient. In each case the upper bound of risk was estimated to be linear at low dose as one would theoretically anticipate.

"It was previously mentioned that the multistage models were approximately linear at low dose rates. An important question is: how good is the linear approximation? It may be that linear extrapolation is a perfectly adequate method and much simpler than using complicated computer algorithms. Furthermore, there is the intuitive belief that the lower convex portion of a typical dose-response curve would be bounded above by a straight line (Hoel *et al.*, (1975). It is felt, however, that a line is a too conservative upper bound in that it greatly over estimates the risk at low dose levels. It has been shown by Crump *et al.*, (1976) that the linear approximation to the multistage model is quite good if a background or spontaneous tumor rate is present." (Hoel, S. 2–4)

Additional technical data are provided in Dr. Hoel's testimony and in references thereto (Albert and Altschuler, 1973; Armitage and Doll, 1961; Cornfield, 1977; Crump *et al.*, 1976, 1977; Guess and Crump, 1976; Guess and Hoel, 1977; Guess *et al.*, 1977; Hartley and Sielkin, 1977; Hoel *et al.*, 1975; Mantel and Bryan, 1961). Other detailed presentations are found in the Reports of the Safe Drinking Water Committee (NAS 1977a, pp. 39–69) and the Food Safety Council (1978, pp. 109–120).

A variety of different opinions has been expressed about the relative merits of the various mathematical models discussed in these sources. The late Dr. Hardin B. Jones (Univ. of San Francisco) took one extreme position in stating that all "true carcinogens" display linear non-threshold dose-response relationships:

"Other substances that may cause cancer are more appropriately called true carcinogens because they show no threshold in the testable dose-risk relationship. The risk they impart is proportional to dose, which is to say, approximately constant in added degree of risk of cancer for each added unit of exposure. True carcinogenesis involves such hydrocarbons as: methylcholanthrene, dibenzanthracene, or benzopyrene. Another example is ionizing radiation." (Jones, S. 3; see also S. 11–13 and Jones and Grendon, 1975, p. 252.)

Dr. Richard Wilson (Harvard Univ.) also proposed that the linear model should be used in risk assessment:

"The preferred technique for simplicity and for a prudent (conservative) public policy is a linear interpolation with no threshold" (Wilson, S. 2; see also Tr. 3422–3423).

Mr. Richard Peto (Oxford Univ.) explained that most models predict a linear dose-response relationship at low dose, because of the probable existence of "equivalent background", *i.e.*, exposure to other background carcinogens to which the effects of an added carcinogenic agent will be linearly additive (Peto, S. 1; Annex B; Peto 1978). He explained during his oral testimony:

"Now, if we admit the possibility of such a background, then it turns out that all the arguments as to whether we should have linear models, K-hit models, one-hit models, probit models, log normal models or whatever, becomes irrevelant to the mathematical estimation of the upper confidence limit on the risk associated with a particular low dose. If any of these models is formulated in the mathematical form that the risk is equal to some function—probit, log normal, whatever—of dose plus background dose, then the consequences will be the same. Where background dose now becomes a parameter to be estimated statistically and if the model is formulated in this way, then we always finish up with linear upper confidence limits; you know, that the risk just turns out to be proportional to the dose at low doses." (Peto, Tr. 2514)

Essentially the same point was made in detail in the original paper by Peto, Hoel and their colleagues in which the multi-stage model was developed (see comment by Hoel quoted above):

"Virtually all models of carcinogenesis that depict the exposure as affecting an already ongoing process will lead to linearity at low dose. We have discussed the validity of this assumption above. This result then implies that, no matter what the biological mechanism we might imagine, if the carcinogen increases some part of the already ongoing process, then we should expect the response to be approximately linear at low dose.

"As pointed out above, this assumption of dependence or common mechanism is not trivial. It can make orders of magnitude differences in the estimated risk associated with low dose exposure.

"If we conceive of the cell alteration process as a series of discrete single-cellular events that can occur in sequence or randomly in any given cell and that a dose-independent induction period follows, then we should expect dose-response over

background to be linear. We have required neither that all steps be affected by the carcinogen (only some) nor that these steps be all mechanistically similar in quantity or quality. This general class incorporates most of the reasonable models that have been proposed. The keys to this result are the assumptions of the single-cell origin and the lack of any appreciable dose dependence in the induction period.

"A further extension of the group of models allows the incorporation of threshold models into the class of "linear at low dose." We have indicated that, if we conceive of single cells as the biological unit at risk and that the initiation response is a threshold phenomenon, then by assuming that the threshold is randomly distributed in dose we find that the low dose response of the whole tissue over background will be approximately linear. If, rather implausibly, we do suppose that some sort of cellular thresholds exist, then clearly all cells do not have the same threshold since all cells do not all become cancers simultaneously. Here again, we have assumed that the carcinogen acts in conjunction with the "spontaneous" or background effects.

* * * * *

"*Practical Implications.* Our results may be crudely summarized by the observation that, in environments already containing appreciable amounts of carcinogenic processes, the effects of any slight addition to these processes will be proportional to the amount added. Both control laboratory animals and wild humans already suffer a considerable incidence of cancer; thus the extra incidence caused by a small amount of a new carcinogen will be proportional to the dose rate of that carcinogen. This thought is not particularly remarkable, but its implications are that much previous investigation of the form of the dose-response relationship at infinitesimal doses is irrelevant to the interpretation of animal studies for the formulation of social policy.

* * * * *

"In our opinion, linear dose-response relationships are likely to be approximately correct for many environmental carcinogens, and this should be publicly agreed for such substances, as it was for radiation 20 years ago." (Crump et al., 1976, pp. 2978–2979; Exhibit 7 to Hoel Statement)

The Report of the Safe Drinking Water Committee also stated that a wide class of multi-stage models leads to predictions of linearity at low doses and that these models have good theoretical justification:

"Most of these theories start with the premise that the carcinogenic process consists of one or more stages that occur at the cellular level, but that not all of these stages are related to the carcinogen. These stages may be cell mutations or other biological or chemical events and may be monocellular or multicellular in origin. The probability of transition to an event related to the carcinogen is assumed to be proportional to the exposure. The exact nature and causes of these events are largely unknown. However, the most important aspect of these quantitative theories of carcinogenesis is that most of them lead to mathematical models for which the probability of tumor occurrence is generally related to a polynomial function of dose. For low exposure, the region of most importance, they are well approximated by a simple linear function of dose (Iverson and Arley, 1950; Fisher and Holloman, 1951; Muller, 1951; Nordling, 1953). This class of dose-response models may be considered as models that are "linear at low dose." Other mathematical dose response models have been proposed for this problem of extrapolating from high doses to low doses, the most notable being the log-probit method of Mantel and Bryan (1961). These types of models have little biological justification in what is known about the carcinogenic process. In addition, some require use of preselected parameters chosen without regard to the particular experimental situation or results. A dose response model selected for extrapolation purposes should, at the very least, be consistent with current knowledge of the carcinogenic process." (NAS, 1977a, p. 47; Appendix I to Rall Statement)

Dr. Arthur Upton (Director, NCI) similarly pointed out that it was a fundamental principle of radiation carcinogenesis that dose-response relationships should be assumed to be linear at low doses. He then stated:

"Accordingly, unless specific exceptions can be demonstrated, it would appear prudent on the basis of present knowledge to apply to chemical carcinogens the four principles listed above for radiation protection." (Upton, S. 7–8)

Dr. Upton stated further:

"I think for purposes of public protection policy, it is generally advocated that one assume a linear dose-effect relationship in the low dose domain." (Upton, Tr. 280)

Other witnesses who gave reasons for preferring the linear and/or multi-stage models for low dose extrapolation included Dr. Joyce McCann (Univ. of Calif.):

"This is, of course, another problem, that because of the confidence limits on the points that we can generate, because they are so wide, they are not inconsistent with other hypotheses. But the linear dose-response is more theoretically pleasing. The Mantel-Bryant really does not have much of a biological basis at all." (McCann, Tr. 1573)

Finally, the NAS Pest Control Committee also recommended use of the linear extrapolation procedure:

"Estimates of Carcinogenic Hazard. Until more is known about the mechanisms of chemical carcinogenesis, any method of extrapolation to predict cancer rates at doses much lower than tested will remain partly a matter of conjecture. However, the single-event hypothesis probably provides an upper limit for induced incidence estimates at low dose levels and is compatible with the very limited human data on carcinogenesis at intermediate response levels. It would therefore seem prudent to employ the single-event hypothesis in making risk estimates, at least for those carcinogens for which the dose-response curve from animal experiments approaches linearity at the lower response levels that can practically be studied. In that case, the estimated total lifetime incidence in man resulting from continuous exposure to an environmental carcinogen would be the lifetime incidence for continuous exposure to the same total dose per body weight found by extrapolation of the animal data under the single-event assumption. For risk assessment, the resulting estimate would then be subject to adjustment to allow for statistical uncertainty in the input data." (NAS, 1975a, p. 85; Appendix H to Rall Statement)

In contrast to this very wide support among experts for the use of linear and/or multi-stage extrapolation models, only a few statements were made in the record justifying the use of other models. Dr. Kelvin H. Ferber (Allied Chemical) expressed a preference for the log-probit model:

"We next address the choice of a dose-incidence model. The logistic model is merely a mathematical convenience with little biophysical support. The one-hit and Weibull models ignore the many defenses (13) available to the organism and frequently lead to absurdly low acceptable dose levels. The lognormal or log-probit model, preferred here, does have a biophysical basis, beyond the fact that many sets of dose-response data fit the model rather closely. At low concentrations, the action of foreign molecules requires work and the rate is thus limited by the well-known work function:

$$W = NRT \ln C_2/C_1$$

from which it follows that the amount of work done, that is, the intensity of attack on a cell or organ is a log function of the available dose. The measureable results of the attack, on the other hand, depend on the susceptibility of the specific organism. It is widely accepted that, in a large population, susceptibility is randomly or normally distributed. This is logical, since susceptibility is influenced by a myriad of physiological, biochemical and genetic factors. (Ferber, S. 3–4)

However, no other witness supported such a relationship between "work" and "intensity of attack." Dr. Adrian M. Gross (FDA) criticized the linear model and introduced correspondence by Mantel arguing that the Mantel-Bryan procedure is better based scientifically (Mantel, 1978; for responses see Cancer Research, 38: 1835)

"Crump's linear model, which is practically identical with the so-called "one hit" model, provides a bound of conservatism to all models for extrapolation into a region of very low rate of response from observable data with the usual size experiments. But the fact that the linear or the one hit model is the most conservative one that could be

conceived does not by itself make it the most desirable one.

* * * * *

"To all this I would add merely a single observation: what distinguishes Mantel and Bryan's (probit) procedure from that of all the other competing proposals is that theirs is the only one to have evolved from considerations of demonstrable realities as opposed to merely mathematical speculation. Basically all of these proposals for risk assessment at very low levels of exposure differ amongst themselves mainly in the steepness of the extrapolating slope. Mantel and Bryan's choice here, one probit per logarithm of the dose, was the result of examining a variety of dose-response relationships in the field of biological assays as was clearly explained in their original paper published in 1961 in the Journal of the National Cancer Institute. They chose this slope in what I would term a "reasonable" fashion, as opposed to a possible anarchistic or nihilistic choice of the most conservative (flat) slope that one could conceive." (Gross, S. 8–9)

One argument presented by Gross was that use of the Mantel-Bryan procedures would tend to promote good experimentation (Gross, S. 10–11). However, Dr. Wilson considered that other low dose extrapolation procedures would do so also (Wilson, Tr. 3433).

The only other detailed discussion of the relative merits of the various extrapolation models was in the report of the Food Safety Council. This report expressed a preference for the multi-hit model, basically on the grounds that this model takes into account empirical evidence for dose-response curves that are steeper than linear in the observable response range:

"5. There are three related but logically distinct elements involved in choice of a method; the choice of a model, the choice of an extrapolation procedure, and a societal judgment as to acceptable risks in the light of possible benefits or lack thereof of the agent under consideration.

"The models that currently seem usable or close to usable for low dose extrapolation are the probit model, the one-hit model, the k-hit model and the Armitage-Doll model. The statistico-pharmacokinetic model, which is in many respects the most biologically realistic of all, is excluded because it appears to require quantitative information on metabolic pathways that will often not be available. The one-hit model is really a special case of the k-hit model and does not require separate consideration. The four dose level experimental design recommended in Chapter 10 will lead to responses permitting the estimation of both parameters of the k-hit model and the control response as well, more often than designs now in use. If the estimated value of k is near unity, this will be equivalent to the choice of the one-hit model, but the choice governed by data rather than a priori considerations. Any of the other three models will describe most data sets in the 5% to 95% range equally well and the choice among them must depend on other considerations, such as the rapidity with which each approaches control, response as dose approaches zero. The probabilities yielded by the probit model approaches zero faster than any power of D, the k-hit model as the k^{th} power of D, and by the Armitage-Doll model slowly, as the first power of D for α, >0.

"A major mathematical basis for this slow approach is the ad hoc assumption that the somatic mutation rate is of the form of $(\alpha+d)$, where D is dosage, α the spontaneous mutation rate (presumably often the result of exposure to physical or chemical carcinogens) and $b>0$. This is a very strong assumption which is not supported by (a) the general lack of evidence for dose-wise additivity shown by many experiments in joint effects of two or more agents, as discussed in Section 2, or (b) experiments in which the effects of one tumor inducing agent inhibits those of another, or (c) experiments, such as those of Hsie et al. (1978) with methanesulfonate in Chinese hamster ovary cells, in which an in vitro linear dose-response curve for mutation disappears when performed in vivo, in agreement with the view that whole body defense mechanisms impair linearity.

"Some agents which are carcinogenic at high dose levels have little or no observed effect at low dose levels, in apparent disagreement with the linear assumption (see, however, National Academy of Sciences, 1977 p. 40). Thus, nitrilotriacetic acid (NTA), which led to kidney tumors in 12 out of 48 rats when fed at 2% in the diet had an incidence of 2 out of 91 at 1.5%, 1 out of 91 at .75%, 0 out of 48 at both 0.2% and 0.02% and 0 out of 127 in control rats. Other high dose carcinogens, considered in the previous section, which show little or no low dose linearity are sodium saccharin, and ethylenethiourea.

"Preliminary results of the experiments of the National Center for Toxicologic Research (NCTR) with 2–AAF show non-zero incidence of bladder tumors at 24 months with 75, 100 and 150 ppm, but none at 4 dose levels below this. The number of animals on whom these preliminary low-dose negative results are based is not given, but the original experimental design called for well above 1,000 animals sacrificed at 24 months or followed for life for each of the four low dose levels (Cranmer, 1978). Results of this type cannot, in principle, disprove the existence of a small but non-zero linearity which eludes detection in experiments of finite size. In this sense, both the concepts of a threshold and of low-dose linearity are opposite sides of the same non-operational coin, neither being generally capable, even in principle, of direct experimental proof or disproof. Mantel's observation and Crump's at least partial agreement (Mantel, 1978) that the additivity assumption leading to low-dose linearity, 'is not a scientifically established fact,' puts the model in its proper perspective—as a hypothesis that may perhaps lead to further experiments or provide alternative explanations for already existing data, but lacking detailed experimental support.

"Some carcinogens yield dose-response curves that are linear or sublinear in the observed dose range, such as vinyl chloride and 2–AAF induced liver tumors in the NCTR results, and for such agents no assumption other than low-dose linearity seems possible. The above argument is critical, not of low-dose linearity when it is justified by the data, but of its assumed general or near-general applicability no matter what the data. What is required is a procedure which assumes low-dose linearity when data in the observable range suggest this, but rejects the assumption when the shape of the curve suggests that the high doses have saturated the repair, protective or other mechanisms by which multi-cell organisms cope with low doses—without, however, assuming the existence of unobservable population thresholds. The gamma multi-hit model has this characteristic, for which reason we recommend its use. There may be special circumstances under which biological considerations not reflected in the observed dose-response curve would suggest low-dose linearity. Nothing that has been said is meant to preclude giving weight to such considerations.

"Many of the extrapolation procedures that have been proposed appear to incorporate value judgments in ways that are not always easily identifiable, particularly in the choice of so-called conservative procedures, such as the use of slopes shallower than shown by the data in the Mantel-Bryan procedure and the use of upper confidence limits to response or lower confidence limits on VSD in both the Mantel-Bryan and Crump et al. procedures.

"Although the value judgment involved in the use of conservative risk assessments may seem appropriate in the light of the many scientific unknowns involved, once formalized as a specific mathematical procedure it escapes the control of the decisionmaker and can lead to undesirable and unsound results by distorting the balance between risk and benefit. We therefore recommend the separation of the mathematical and societal aspects of the problems, with the extrapolation procedure chosen to provide 'best estimates' of risk as well as their upper or lower limits. The behavior of confidence limits in the absence of any evidence of toxicity, as discussed in the previous section, provides another reason for confining the extrapolation procedure to best estimates." (Food Safety Council, 1978, pp. 116–117; Hearing Exhibit 227)

Although this is one of the most recent reviews of the problem, no witness at the hearing expressed support for the scientific and judgmental views expressed in it.

Several witnesses recommended that dose-time relationships should be taken into account: Dr. Kelvin Ferber (Allied Chemical), S. 4–7; Dr. Hardin Jones (Univ. of San Francisco), S. 3–4; Dr. John Zapp (DuPont), S. 14–23; and Mr. Carroll Weil (Carnegie Mellon Univ.), S. 3–5. However, there is considerable doubt that any general relationship between dose and latent period would be applicable to humans (for full discussion see the Section on No-Effect Levels above). This point was discussed by Peto (S. 1, 6–7) who concluded that the

evidence cited for a relationship between dose and latent period is faulty, and that under the multi-stage model no such dependence would be expected:

"Failure to allow for the numerical effects of competition to be first (and the consequent failure to realize that such a competition ceases to have any material effects once the expected number of tumors per animal decreases below about 0.1) is a common error (Jones and Grendon, 1975; 1976). A much more common, and much more serious, error is failure to remember that no carcinogen acts alone, and that the effects of background processes place another substantial constraint, completely ignored in the testimonies of Professor Hardin Jones and Dr. Weil, on the effects of progressive dose reduction on the age distribution of those tumors which do arise. As I have already explained, the simple assumption of the existence of some background exposure suffices to demonstrate that all mathematical and biological hypotheses yield predictions which conform with the principles with which I started: proportionality of extra risk to applied dose, and independence of age distribution from applied dose." (Peto, Annex B, S.30).

This point was also addressed by Dr. Hoel:

"Most dose-response studies in animal experimentation are plots of dose rate versus total tumor incidence for the duration of the study. In large studies there is often sufficient data to plot cumulative tumor incidence versus age. This is then done for dose and the curves compared. Models are also fit to data and have the possibility of use in low dose estimation. Albert and Altshuler (1973) have fit the log normal model of Blum and Druckrey to several sets of laboratory data. Also Whittemore and Altshuler (1976) have fit both the Weibull and log-normal model to the physician smoking data of Hill and Doll. As with the ordinary dose-response models one finds that there usually is not sufficient data to distinguish between competing models. Yet the choice of a time-to-tumor model can greatly change any estimated low dose effects.

"It has been suggested (Jones and Grendon (1975)) that the time to first tumor or latency period increases with decreasing dose. Then with a sufficiently small dose the time-to-first-tumor will exceed man's lifetime thus producing an effective carcinogenic threshold. Unfortunately as shown by Guess and Hoel (1977) the observed time-to-first-tumor will increase with decreasing dose for the multistage model yet no true threshold will occur at low doses with this model. In other words a non-threshold model will predict that the data will look as though a threshold in time exists, when in fact it does not." (Hoel, S. 6–7)

Dr. Hoel discussed this issue further in his oral testimony:

"Now, at one time, people felt that, well, if you bring time into it, then we can solve our problems because you can get the accurate estimates, but the situation is the same both whether you use time or you do not use time, that you could fit the models equally well and you get quite different answers in the low-dose region. Therefore, your models should have a biological basis and not simply be a curve-fitting exercise." (Hoel, Tr. 2151)

A more technical discussion of the issues was given earlier in a paper by Hoel *et al.* (1975), who pointed out the difficulties in selecting an appropriate time-to-occurrence model and drew the following conclusion:

"With both lognormal and Weibull models there are considerable technical problems in the actual estimation of the unknown parameters. These become particularly complicated in the face of competing risks. If these statistical difficulties can be satisfactorily overcome, extrapolation could then be considered. Again, as expected, low dose extrapolation is highly dependent on the choice of which of the two models to apply. One set of calculations in Chand and Hoel (1974) gave differing values for the probability of tumor occurrence in a particular hypothetical experimental situation. At a given low dose it was found that the lognormal model predicted an incidence of $2X10^{-7}$, while the Weibull model yielded, at the same dose, an incidence of $2.4X10^{-4}$. The magnitude of the difference increased as the dose level decreased. This is qualitatively the same as, but quantitatively even more difficult than the situation with the dichotomous response model. Also, it is not clear whether these differences are primarily due to the manner in which the dose dependency was incorporated into the model or the distribution which was chosen, or both. Thus it may be concluded that the problems of model dependency in low dose extrapolation will be present in both the dichotomous and time-to-occurrence situations.

"Research is needed to solve the difficulties which occur in order to obtain conservative models for required extrapolation in time-to-occurrence situations. This may be possible by using the Weibull distribution with particular restrictions on its range of parameter values. Considerable investigation is needed before time-to-occurrence models can be seriously used in establishing maximum risk associated with exposure to low dose levels." (Hoel et al., 1975, p. 144; Exhibit 14 to Hoel Statement)

OSHA concludes from this expert testimony that the scientific basis for assuming relationships between dose and time-of-occurrence in the low dose region is tenuous, and that the simple formulae proposed by certain witnesses are not well supported. At the present time, it would be premature to attempt to incorporate dose-time relationships into low-dose risk extrapolations.

The above discussion has been limited to the question of low dose risk assessment based on extrapolation of animal data. In special cases it may be possible to extrapolate from epidemiological data in exposed humans. However, such cases are rare because quantitative data on dose-response relationships are rarely available, and only a few witnesses even mentioned such extrapolations. These witnesses explicitly or implicitly assumed that linear dose-response relationships would be a valid basis for extrapolation, and no witness specifically contested this assumption.

Dr. Joyce McCann (Univ. of Calif) presented data on lung cancer in human cigarette smokers, which agree very closely with a linear dose-response relationship over an 8-fold range of doses (McCann, S. 19–20, Fig. 2). The same data were presented in the OTA Saccharin Report (OTA, 1977, p. 23) and discussed by other witnesses: Mr. Richard Peto (Oxford Univ.), S. 10; Dr. Richard Wilson (Harvard Univ.), S. 13–14; and Dr. Ian Nisbet, Post-hearing Comment, pp. 3–4. Dr. Richard Wilson (Harvard Univ.) presented risk estimates for several carcinogens by linear extrapolation from epidemiological data (S. 50–51, 53, 76–81, 84–86; Hearing Exhibit 251B) as did Dr. Ian Nisbet (Post-hearing Comment, pp. 1–7; Hearing Exhibit 224e). No objections were made to such procedures, which appear reasonable in the light of the data presented on smoking.

A complicating factor in extrapolating from human epidemiological data is that in most cases such data refer to persons exposed for a limited fraction of their lifetimes. Several witnesses have pointed out that the incidence of most human cancers increases as the k'th power of age, where k is between 2 and 8 and is usually 4 or 5. Discussion on this point was presented by: Dr. David Hoel (NIEHS), S. 4–7; Dr. Francis J. C. Roe (AIHC), S. 50–51; and Mr. Richard Peto (Oxford Univ.), S. 10. Accordingly data based on exposures for even half a lifetime (35 years) will greatly underestimate the potential effects. This question was discussed in the NCI, NIEHS and NIOSH Institutes' Report (Hearing Exhibit 224b, Appendix A). In this report it was concluded that for most carcinogenic agents, the excess risk would remain even after exposure was terminated. Exceptions to this generalization would be agents such as cigarette smoke which act at late stages in the carcinogenic process. For such agents, the relative risk of induced cancer may decrease towards 1 after cessation of exposure (ibid.) Thus, unless there is reason to assume that a particular carcinogen acts at a late stage, measurements of risks after half a lifetime's exposure are likely to underestimate lifetime risks by a factor of 16–32 or even more.

4. Scaling Factors for Extrapolating From Animals to Humans

If one of the above mathematical models is used to estimate potential low dose risks by extrapolation from high-dose observations in animals, the estimates strictly apply only to the same species of animal under the same experimental conditions. To estimate potential low dose risks to exposed humans, additional assumptions have to be made about relative risks to humans and animals at low doses. Much testimony was presented in the hearing about these assumptions and the uncertainties resulting from their adoption.

The first set of assumptions relates to scaling factors. A human, for example, lives for 35 times as long as a mouse, and has roughly 3,000 times as many cells, so that over a lifetime the chance of one cell being "hit" by a carcinogen is 100,000 times higher for a human than for a mouse (Hart, S. 23–28; Rall, 1977, Appendix E to Rall Statement). How are such factors (and other scale factors such as differences in rate of metabolism and rate of cell division) to be taken into account in extrapolating from one species to another?

This question has been addressed in several reports. The Food Safety Council discussed the theoretical issues as follows:

"The two main methods for converting results in experimental animals to man are on a mg/kg/day body weight basis or by the concentration in the diet. When the experimental animal is the mouse, dietary concentration leads to a VSD for a man 6-fold lower than that obtained with the mg/kg conversion (Assoc. Food and Drug Off., 1959). Dietary concentrations are not considered accurate indices of actual dosages since the latter are influenced not only by voluntary food intake as affected by palatability and caloric density of the diet and by single or multiple caging, but more particularly by the age of the animal. During the initial stages of growth, the anatomic, physiological, metabolic and immunologic capabilities are not fully developed. Moreover the potentiality for toxic effect in an animal is a function of the dose ingested, utimately the number of molecules per target cell which would indicate that actual intake in mg/kg/day rather than dietary concentrations should be the basis for inter-species conversions." (Food Safety Council, 1978, p. 118; Hearing Exhibit 227)

Dr. Hoel and his colleagues discussed the same points in an exhibit to Dr. Hoel's testimony:

"The extrapolation of the results from laboratory animal studies to man is probably the most difficult and least understood aspect of the total extrapolation problem. There is generally good qualitative agreement between carcinogenesis in animal and in man. The difficulty arises in attempting to predict quantitatively from animal data to man.

"For acute toxicity of a number of anti-cancer agents, parameters such as the LD_{10} and maximum tolerated dose are quantitatively quite similar in mouse, rat, hamster, dog, monkey, and man (see Freireich et al., 1966). This similarity was observed when the dose was administered on a basis of surface area which is approximately equivalent to using the 2/3 power of weight. On a basis of dose per unit of body weight, man would be about 12 times as susceptible as the mouse (see Rall, 1969). If dosage is, however, on a dietary-concentration basis, then it has been suggested that there is little or no further need to make a surface area adjustment (Mantel and Schneiderman, 1975).

"Little is known quantitatively about comparative chronic toxic effects in animal and man. For a given compound there are likely to be species differences in absorption, metabolism and excretion which must be taken into account in quantitative extrapolation. At the present stage of knowledge the prudent strategy, after performing extrapolation, would be to incorporate a conversion factor based on the 2/3 power of weight and an additional species factor. This species conversion factor should be determined by biological considerations after taking into account the compound and the available information concerning the species and strain being tested." (Hoel et al., 1975, pp. 145–146; Exhibit 14 to Hoel Statement)

Another discussion of the issue was presented in the Report of the Safe Drinking Water Committee:

"Size tends to determine the rate of distribution of substances in the body; in large animals, they are distributed more slowly and tend to persist longer. In general, large animals metabolize compounds more slowly than do small animals. Large mammals have many more susceptible cells; thus, if the carcinogenic event is rare, it would be more likely to occur in a large mammal than in a small one (a mouse experiment using 1,600–2,000 animals represents about the same number of susceptible cells as are contained in one man). Obviously, however, a mouse is not the equivalent of a very small man; nor is a man the equivalent of a very large mouse. In the mouse, the ratio of cardiac output per minute to blood volume is 1:1. In man, the ratio is 1:20. Thus, blood circulates approximately 20 times as rapidly in a mouse as in a man. (This difference is not a peculiar species difference, but typifies the differences between very small and relatively large animals.) The implication is that the time a substance spends in the plasma (excluding metabolism) is longer in a larger mammal than in a smaller one. Thus, for the same milligram-per-kilogram dose, human tissues are exposed to a substance for a much longer time than mouse tissues. This is consistent with data obtained in studies of anticancer drugs, which showed that—on a milligram-per-kilogram basis—a mouse required 12 times as much drug to respond as did man, a rat 6 times as much, and a dog and a monkey 2–3 times as much. When the data were expressed on a milligram-per-square-meter basis, the differences between species were sharply reduced. In addition, the cell-division rate is greater in small animals: e.g., the cycle time of mouse gut or marrow cells is about half that of man. The life span of a man is 35 times that of a mouse. Thus, there are many more cell divisions in man, and therefore a greater opportunity for neoplastic change.

"These observations suggest that small mammals that are routinely used for toxicity testing are often more resistant than man to toxic compounds. This implies that small animal systems are likely to produce many false-negative results, and has important implications for establishing safety factors or using "conservative" techniques for extrapolation." (NAS, 1977a, pp. 31–32; Appendix I to Rall Statement)

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"Various measures used in assessing acute toxicity—such as LD_{10}, LD_{50}, and maximal tolerated dose—are generally found to be quantitatively similar among most animals. On the basis of dose per unit of body surface, toxic effects in man are in the same range as those in experimental animals, such as mouse, rat, hamster, dog, and monkey. On a body-weight basis man is generally more vulnerable than the experimental animal; probably by a factor of 6–12. Comparative studies have shown generally that absorption, metabolism, and excretion of various drugs are slower, dose-for-dose, in man; that there is greater retention of such drugs; and that higher concentrations occur in body fluids and tissues in man than in small mammals" (*ibid.* pp. 52–53).

Empirical data to clarify the question of interspecific scaling of doses for carcinogenic effects are extremely scanty. Dr. Matthew Meselson (Harvard Univ.) and Dr. Donald Kennedy (Commissioner, FDA) presented an analysis of dose-response data in animals and humans for six carcinogens, published as part of the NAS Pest Control Report:

"The carcinogens for which comparisons can be made are those already known to affect humans. In generalizing to other compounds, this selection may impose a bias, exaggerating the sensitivity of man relative to laboratory test systems. Other factors may introduce an opposite bias. For two carcinogens, vinyl chloride and DES, observations on man are for considerably less than a full lifetime so that the reported incidence may be a serious underestimate of the eventual total. Also, these two compounds and aflatoxin are known as human carcinogens because they are associated with types of cancer that are otherwise rare. If these carcinogens also induce more common types of cancer, even at much higher frequency, this could go undetected, again giving rise to an underestimate of their overall carcinogenicity to man.

"The limited conclusion that emerges from the comparisons given in Table 5 is that if the data from the most sensitive published test on animals are used to predict lifetime human

incidence on a dose per weight basis, the results seem approximately correct for benzidine, chlornaphazine, and cigarette smoking. For aflatoxin, the predicted human incidence is about ten times greater than estimated from existing epidemiologic studies, while for vinyl chloride it is about 500 times higher. For DES, the human incidence predicted from the result of a single dose administered to newborn female mice is about 50 times higher than that estimated from studies of adenocarcinomas in daughters of women given DES during pregnancy. Thus, as a working hypothesis, in the absence of countervailing evidence for the specific agent in question, it appears reasonable to assume that the lifetime cancer incidence induced by chronic exposure in man can be approximated by the lifetime incidence induced by similar exposure in laboratory animals at the same total dose per body weight. (For a discussion of interspecies scaling factors for dose, see Rall 1974.)" (NAS, 1975a, p. 82; Appendix H to Rall Statement)

This conclusion was quoted by several other witnesses. In opposition to this conclusion, Dr. Wilson (1978, Exhibit 51) reanalyzed the data for the carcinogens reviewed by the Pest Control Committee and claimed that the dose-response data in animals and humans corresponded better when scaled on the basis of mg/kg/day rather than mg/kg/lifetime (see also Wilson, S. 21). In other words, Dr. Wilson's analysis suggested that animals and humans would suffer generally similar risks if exposed to the same carcinogen, each at the rate of 1 mg/kg/day; on the other hand, the NAS analysis would suggest that humans exposed to a carcinogen at 1 mg/kg/day would suffer similar risks to rats exposed at 35 mg/kg/day. There are problems with both interpretations: under the scaling rule proposed by NAS, human risks might be overestimated by factors up to 200 (vinyl chloride, diethylstilbestrol), whereas under Dr. Wilson's scaling rule, human risks might be underestimated by similar factors. OSHA is inclined to place more weight on the NAS analysis because, as stated in the NAS report, the human data on vinyl chloride and DES used in the analysis probably represented only part of the lifetime response to these carcinogens. However, even without resolving the discrepancy, it is apparent that scaling factors alone introduce considerable uncertainties in predicting human risk from animal data, perhaps by a factor of at least 35. OSHA is aware of the fact that the NAS analysis is based on an extremely small number of cases, which include poorly controlled studies and offer a tenuous basis for any quantitative assessment of the results.

5. Factors Complicating Extrapolation From Animals to Humans

In addition to scaling factors, there are many other factors which complicate the extrapolation from animal data to predict the potential magnitude of risks to humans. Some of the complicating factors mentioned at the hearing include metabolism and pharmacokinetic factors (including differences in rates of absorption, distribution, metabolism, and excretion); dose-dependent pharmacokinetics; inter-species, inter-strain, and inter-individual differences in metabolism and susceptibility; additive and synergistic interactions with other carcinogens, co-carcinogens, hormonal and immunological factors; prenatal and neonatal exposure; DNA repair; differing routes of exposure; etc.

These points were addressed in a number of statements, comments, and exhibits, of which the following provide only a sample. The Safe Drinking Water Committee discussed the problem as follows:

"Number of Animals

"The number of exposed animals is important. Typically, about 10^2–10^3 experimental animals are tested, whereas the population of humans to be protected may be 10^8–10^9.

"The human population is genetically heterogeneous, whereas test populations of animals, as a rule, are relatively inbred. Genetic traits can affect many aspects of susceptibility to pollutants.

"Selectivity influences the test-animal population in that only healthy vigorous animals are started on test, whereas the exposed human population may contain subpopulations that are ill and weak.

"Environmental Differences

"Nutritional differences and the physical environment (heat, light, ionizing radiation, etc.) can affect response to pollutants. The chemical environment—from drugs to air pollutants—with its overwhelming number and types of substances, provides the possibility for synergistic toxicity. Synergistic effects have occurred with therapeutic drugs, are well known in experimental carcinogenesis, and are an ever-present danger.

"Absorption

"Rates of absorption of chemicals through the gastrointestinal tract are generally comparable in laboratory animals and man. The barriers within the gastrointestinal tract and the cell membranes, which prevent the free passage of organic compounds, are quite similar among mammalian species. These barriers are either the cells themselves or the intercellular junctions, which are "closed" or "tight" and which, in general, force substances to move through cells, rather than between them. It should be recognized, however, that there are differences between one animal and another and between man and animal. The ratio of surface area to volume in the gastrointestinal tract, and the transit time through it, often differ among and within species. These factors affect absorption. The pH differs in various parts of the gastrointestinal tract in different species; this can affect the absorption of some partially ionized compounds. The possibility that intact proteins can be absorbed in neonates of some species suggests that absorption in the neonate can be nonspecific.

"The presence of bacteria in the gastrointestinal tract can affect absorption indirectly. Bacteria may convert the original substance into one that is more or less absorbable, and thus alter the apparent toxicity of a chemical, or they may convert a nontoxic substance into a toxic one. For example, reduction of nitrate to nitrite permits the formation of highly carcinogenic nitrosamines by reaction with secondary amines from the diet. The bacterial populations in the gastrointestinal tract vary between species and within species, and in the same individual from time to time, often changing with changes in diet.

"Distribution and Storage

"Once a compound is absorbed, it is distributed throughout the body, largely by the circulatory system. This gives the opportunity for binding to plasma protein or tissue, and storage in such depots as fat and bone. There can also be differences between species with respect to plasma protein and tissue binding. These differences do not seem to be of major importance, but small mammals, such as mice, tend to bind substances less extensively than man. Research on such subjects as storage depots is needed.

"Metabolic Differences

"The primary organs that metabolize substances are the liver, the lungs, and kidneys. With respect to hepatic metabolism—often considered to be the most important—small mammals generally metabolize substances more rapidly than large mammals, and herbivores more rapidly than carnivores. There are other interspecific differences; this is a field in which research is active.

"Excretion and Reabsorption

"There are few comparable data contrasting renal or hepatic excretory rates of substances in mice, rats, dogs, monkeys, and man. What data there are suggest that small mammals excrete compounds via the kidneys considerably more rapidly than large mammals. There are too few data to show systematic differences in hepatic excretion and the extent of reabsorption after hepatic excretion. Some substances are excreted through the hepatic system more rapidly by rodents than by dogs and other large animals. After excretion via the bile, reabsorption from the gastrointestinal tract may occur.

"Differences in Receptor Sites

"The action of cellular and intercellular membranes is also of concern. An unaltered substance or its metabolites, after distribution through the body, must pass through a variety of cellular and intercellular membranes to arrive at the site of action. Many of these membranes are of major importance in determining the ultimate

toxicity of the substance. The blood-brain and blood-testicular barriers, for instance, effectively modulate the chemical composition of the fluid surrounding the central nervous system cells and the developing sperm cells. These barriers can also avert or delay the arrival of potentially toxic compounds at the sites of action. Similarly, the placenta acts as a barrier between the maternal circulation and the developing fetus. In addition to the passive barriers, active-transport systems influence the movement of foreign organic compounds. This is a subject in which research is moving rapidly, and there is a great need for unified systematic theories on interspecific relationships. In general, if a substance reaches a site of action, the ultimate toxic reaction seems to be consistent among species. Development of a lesion will then follow this reaction. With some of the more serious manifestations, such as malignant change and mutagenic change, development of a lesion may depend on the extent of damage (e.g., severely damaged cells will die; generation time of the cells and rates of repair processes may be affected). For instance, the generation time of the rapidly proliferating cell population in the mouse is about half of that in man; therefore, cancer is likely to appear earlier in the mouse."

* * * * *

"More and more patterns that are useful for extrapolation to man are being recognized and can be identified in the course of studying pharmacological disposition of a substance. Most of the differences that have been observed suggest that man is more sensitive than the usual experimental animal, and this must be kept in mind in establishing permissible exposures for humans.

"There are great difficulties in comparing the median animal to the not-so-average man. Man is not genetically homogeneous and is usually exposed to a much wider range of environmental conditions than the usual experimental animal. Differences in environmental factors are known to affect the toxicity of a substance. Differences in the genetic makeup of the individual can affect toxicity. These must be considered in the extrapolation of laboratory-animal toxicity data to man. We must predict for, and protect, the highly sensitive individual as well as the average or median person. Because of the multitude of man-made chemicals, the different habits and life-styles of populations, and the different eating habits of populations, there is considerable variation in the intake of, or exposure to, environmental pollutants. These must also be considered in establishing permissible exposures to environmental agents.

"In the last decade, large genetic differences in metabolism of toxic agents have been found in man, and study of these effects has led to a new branch of pharmacology—pharmacokinetics. The range of variability is illustrated by the observation that, in a group of about 20 patients, the steady-state plasma concentrations of two tricyclic antidepressants varied by about 30-fold, and the half-time of disappearance from the plasma varied about 10-fold (Hammer and Sjoqvist, 1967). Also, the plasma concentration of isonicotinic acid hydrazide has been found to vary by a factor of almost 100 in different people, and this appears to be genetically controlled (Weber, 1976).

"Many examples of unexpected toxic reactions to therapeutic agents have been caused by interactions of compounds that were normally safe when given alone (Conney and Burns, 1972). The likelihood that such synergistic interactions will occur with environmental pollutants is high. An early and striking example of unexpected synergistic interactions (hypertensive crisis) occurred in patients who, while taking monoamine oxidase inhibitors, ate cheese that contained bioactive amines. Although theoretically predictable, this effect had not been suggested in the literature before it was observed in patients.

"Many sources of variation within the population of any species, such as age, sex, pregnancy, disease, can affect the response to foreign substances. An example is the difference between sexes in metabolism and toxicity of acetylsalicylic acid (Menguy et al., 1972).

"In addition, such environmental variables as temperature, lighting, barometric pressure, humidity, and diet are known to affect the toxicity of environmental pollutants. For example, the oral absorption of pentobarbital is greatly altered by the prior ingestion of a small cheese sandwich. In this case, peak pentobarbital concentration in plasma is diminished by about 50%, and the duration of the effective plasma concentration is doubled (Bush et al., 1966).

"Another difficulty in extrapolating from laboratory animals to man is the dose-duration problem. The lifetime of a mouse is about 2 yr. A man's life expectancy is close to 70 yr, and a woman's 5 yr longer. Because man usually excretes compounds more slowly than mice, this means that man, with a very small daily intake, can develop a greater accumulation of a compound over many years.

"It is currently impossible to estimate the effects of all the genetic and environmental variability in the human population."

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"In all these [extrapolation] theories, the emphasis is mainly on the stochastic nature of the changes involved in the carcinogenesis process. The role played by the carcinogen is considered to a much lesser degree. It is commonly assumed that transitional events in the process that are attributable to the carcinogen occur with probabilities proportional to the degree of exposure. This is undoubtedly a gross oversimplification of the actual process. The actual exposure is no doubt modified by absorption, distribution, metabolism, and excretion of the chemical substance, and the effective exposure should probably be the actual concentration of the carcinogen at and within the target cells. Other factors that may affect delivery of the carcinogen to intercellular compartments are membrane permeability and enzyme binding. Therefore, the "effective dose" may well be some complex function of the actual exposure and the biochemical and physiological characteristics of the host. Most of these mathematical models incorporate the dose as it is actually administered in animal experiments or human exposure. The function relating administered dose to "effective dose," if it is not a simple case of proportionality, can have a profound effect on the dose-response relationship. As a simple example, consider a linear model relating dose (effective dose) to response. If the effective dose is proportional to the administered dose, then a linear model obtains for administered dose versus response. If the dose relationship is concave, which would obtain if the incremental increase in effective dose decreases with higher doses, then the relationship between administered dose and response would also be concave. Thus, the various dose-response curves that have been observed may not be indicative of different carcinogenic processes once the agent has reached the target cell, but rather may indicate different functions relating administered dose to effective dose. This problem will probably relate more to chemical cacinogenesis as opposed to radiation-induced cancer." (NAS, 1977a, pp. 32–36, 41–42; Appendix I to Rall Statement)

The International Agency for Research on Cancer (IARC), in the revised preamble to its monograph series, also noted that extrapolation from one species to another introduced unquantifiable uncertainties:

"In the present state of knowledge, it would be difficult to define a predictable relationship between the dose (mg/kg bw/day) of a particular chemical required to produce cancer in test animals and the dose which would produce a similar incidence of cancer in humans. The available data suggest, however, that such a relationship may exist,[46] at least for certain classes of carcinogenic chemicals. Data that provide *sufficient evidence* of carcinogenicity in test animals may therefore be used in an approximate quantitative evaluation of the human risk at some given exposure level, provided that the nature of the chemical concerned and the physiological, pharmacological and toxicological differences between the test animals and humans are taken into account. However, no acceptable methods are currently available for quantifying the possible errors in such a procedure, whether it is used to generalize between species or to extrapolate from high to low doses. The methodology for such quantitative extrapolation to humans requires further development." (IARC, 1978, Vol. 17, p. 20)

The National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis discussed the complexities of interspecies extrapolation in the following terms:

"*Quantitative extrapolation* from animal studies for the purposes of evaluating human risks entails large uncertainties at the present time. Each case must be individually evaluated, taking into consideration such factors as adequacy of experimental design, statistical significance of the data, dose-response relationships, duration of exposure, route of administration, metabolism (including species variations), host's susceptibility, co-factors and other modifying

factors, and the amount of the material to which humans will be exposed. The criteria for extrapolation may vary depending on the agent in question." (NCAB Report, 1977, p. 463, emphasis supplied)

Dr. Harold Stewart (NIH) introduced the report of an Ad Hoc Committee on Testing for Environmental Chemical Carcinogens, which reported to the Director of NCI as follows:

"In forming judgments as to the possible carcinogenic hazard posed by a particular environmental chemical, consideration must be given to certain important aspects of the action of these agents. These include, among others: the long latent period; the wide variation in individual susceptibility and degree of exposure; the possibilities of exposure transplacentally (fetus) and via the mother's milk (newborn); the potential of most chemical carcinogens for producing cancer of various organs under different circumstances, the additive, synergistic and antagonistic actions of many carcinogens, the virtual irreversibility of effects of submanifestational doses; the importance, to the ultimate development of cancer, of the totality of lifetime exposure to all carcinogenic agents, chemicals, radiation and viruses. . . .

"In view of the wide differences in susceptibility to potent chemical carcinogens of different species, strains, and even individuals of the same species, the extent of hazard for man cannot possibly be judged on the basis of dosage requirements for carcinogenicity in any other species. Moreover, it is impossible, on the basis of findings in other species, to evaluate the significance for human cancer of carcinogens that reach the fetus by transplacental passage or the newborn by way of the mother's milk.

Furthermore, carcinogenesis in man probably involves actions of a number of agents, perhaps in the hundreds, some operating simultaneously and some sequentially, on an extremely heterogeneous population. Some of these may act additively, others synergistically, and still others antagonistically. Isolation of a single one or a few for analysis in animal experiments tends to produce a caricature of the human situation which may be misleading.

"There can be no question of the value of investigating carcinogenicity at different dose levels of the agent. For example, information as to mechanisms of action and the influence of modifying factors might be better obtained with minimally effective than with maximally tolerated amounts. However, this is not relevant to identification of environmental carcinogens and assessment of their significance for human cancer, which are our immediate concerns. Moreover, in the case of many, if not most, carcinogens, decreasing the dosage from a maximally effective to a minimally effective level produces prolongation of the latent period in addition to decreased incidence of tumors. If latent period exceeds the life span of the animal, negative results may be obtained at levels that might be carcinogenic for equally susceptible, longer-lived animals.

"If one plots the incidence of tumors against time at any given dose of carcinogen, one finds considerable variation in the latent period in individual animals, even of inbred strains. The variation is greatest at low dose levels, because large doses are able to override the effects of small genetic or experimental variations. This is one of the reasons for employment of maximum tolerated doses in testing for carcinogenicity. As the dosage is lowered, tumors appear only among the more sensitive animals. In the case of the human population, with the completely unknown variations in sensitivity to any chemical carcinogen, and with the impossibility of knowledge of other variables that may affect responsiveness to these agents, attempts to establish threshold levels for carcinogenicity are unrealistic.

"Of major importance in this connection is the fact that the carcinogenic process initiated by a submanifestational dose of one agent may be brought to completion by a submanifestational dose of another agent of entirely different chemical structure, even when exposure to the first agent has ceased and even when long periods of time intervene between the two types of exposures. It appears that carcinogenesis can result from the summation of a number of irreversible alterations in cells, no one of which may suffice to produce a manifest cancer. This is known to be true of the carcinogenic effects of ionizing radiation; it is the total lifetime exposure that is the determining factor. Similarly, there is no evidence that a newborn animal exposed to a chemical carcinogen ever reverts to normal with respect to the likelihood of developing cancer. On the contrary, throughout its lifetime it has a higher risk of developing cancers then its untreated littermates.

"Under natural conditions, few if any people are exposed to a single pure chemical. Such exposure is usually to mixtures and crude products. Isolation of individual carcinogens is often complicated by the presence of other chemicals that can enhance or retard the carcinogenic reaction. For example, the role of such co-carcinogens and/or anticarcinogens in tobacco smoke may be as important as that of the several carcinogens that have been isolated in minute quantities.

"There can be no doubt that the general population is continually exposed to hundreds of chemical, physical and biological agents that produce cancers of various types in various species under certain conditions. Little is known about interactions between several of these agents, but there is clear evidence that such interactions do exist. Additional complexities are introduced by evidence of involvement of intestinal bacteria in metabolic conversions of the active carcinogen in cycad meal.

"In view of the enormous and largely unpredictable differences in susceptibility of different species and different individuals to most carcinogens, and the fact that the significant factor is the totality of lifetime exposure (which can never be estimated accurately) to a large number and variety of carcinogenic agents and cocarcinogens, some known and many unknown, little if any useful practical purpose can be served by attempts to assess the hazard for man of a particular environmental carcinogen on the basis of quantitative data obtained in laboratory animals. Emphasis on this point not only is misguided but is misleading and may be harmful." (Stewart, S. 2–5, quoting from NCI, 1973; Hearing Exhibit 14)

Several other witnesses discussed factors complicating quantitative extrapolation. Dr. Curtis Harris (NCI) and Dr. Benjamin Trump (Univ. of Md.) presented the results of their own studies which have shown marked inter-individual differences in the metabolism of procarcinogens to their ultimate metabolic forms. These differences are believed to correlate with differences in susceptibility, as Dr. Harris explained:

"From the quantitative point of view a wide interindividual variation in the levels of carcinogen-DNA adducts has been found. For example, the inter-individual variability for binding levels of benzo[a]pyrene to DNA was 70-fold for cultured human bronchus and nearly 100–fold for cultured human colon (6, 13). A marked variability among individuals is also found in pharmacological studies of drug metabolism in clinical studies (14). The clinical pharmacology of drugs metabolized by mixed-function oxidases have particular importance and relevance to the metabolism of carcinogenic polynuclear aromatic hydrocarbons because they also require oxidation by this class of enzymes to become ultimate carcinogens. One of the mixed-function oxidases, aryl hydrocarbon hydroxylase, is under genetic control in mice (15). Recent investigations of aryl hydrocarbon hydroxylase in cultured human monocytes and lymphocytes from twins have also found a major genetic component of control and have suggested that the pattern of inheritance is polygenic (16). Aryl hydrocarbon hydroxylase activity has been found in several other human cells and tissues, e.g. liver, pulmonary macrophages and placenta (17, 18, 19, 20). Environmental factors such as tobacco smoke and chemicals can also have a profound effect on the activity of mixed-function oxidases including aryl hydrocarbon hydroxylase (14, 17). For example, smoking of tobacco by women enhanced the activity of placental aryl hydrocarbon hydroxylase (19). However, a marked variation in enzyme activity was still associated with a relatively constant level of smoking; a 70-fold variation was found in placentas from women who smoked 15–20 cigarettes per day (20). The interaction between genetic and environmental factors in the control of carcinogen metabolism is still largely undetermined, but methods have been developed in the last decade to make this a fruitful area for future studies." (Harris, S. 3–4)

In his oral testimony, Dr. Harris (NCI) discussed the significance of these and other findings:

"If you compare different strains of a species, you can get marked differences in the kinds of test results that we are doing, such as binding to DNA. In some cases, this correlates with susceptibility in the test

animal. We have no evidence yet that it will correlate with susceptibility in humans, although we suspect and we hope that it might. (Harris, Tr. 2018)

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"Now, one of the great deficiencies we have in our experimental data is that we look primarily at only one compound at a time in the experimental test, where we know that humans are exposed to multiple agents at different levels in different regimens, and the interaction may be quite complex. In fact, we know of synergism between carcinogens such as tobacco smoke and asbestos. The people who happen to be exposed to asbestos and smoke cigarettes have a markedly greater risk of developing lung cancer, bronchogenic carcinoma—and I think we have to be very careful about what we mean by lung cancer—than the smokers here in this room. The asbestos, I understand from Dr. Selikoff, itself has some effect in increasing the risk of bronchogenic carcinoma, maybe four or fivefold, which is significant. But the risk of asbestos alone and the risk of cigarette smoke alone is more than additive, and I think that is a—and there are other examples—that is a warning sign.

"Our experimental tests are at the point that we are not looking at these interactions now in testing compounds. I think that more effort ought to be put in this area. But there are differences in strains, there are differences probably in people. But I think the question you really want to ask is, are there thresholds; are there thresholds in carcinogenesis, and at the moment we have no method of determining thresholds and there is no evidence for that. Unfortunately, most of our tests, our animal testing, is a very insensitive system for a variety of reasons that I am sure there has been testimony given here on the number of animals that are under test, the fact that there are examples in which the human seems to be more susceptible to a compound than any animal species. Beta-naphthylamine is a good example. That is why I think we have to be very hesitant in making quantitative extrapolations. I do not think we can do that. Beta-naphthylamine for workers who have been exposed to that compound for over a five-year period causes 100 percent bladder cancer. Now you would not have never predicted that from the animal tests. You would not have predicted its potency. And that is very unfortunate. I wish we had test systems in which we could predict potency, but we do not." (Harris, Tr. 1973–1975)

Dr. Arthur Upton (Director, NCI) made the following comment:

"Such evidence as we have does lead us to suppose that there may be enormous variations in potency, million-fold differences in potency, that aflatoxin being one of the most potent carcinogens in animals, and trichloroethylene being perhaps 100,000 or a million times less potent.

"But the evidence is still fragmentary. We need much more research before we will be in a position to speak confidently about potency.

"There is the other problem that in the experiments that we have done, it has been customary to give one compound at a time to the test animals, and we have good evidence that combinations may produce unpredictably large effects. *So an agent which may not be potent alone may in the presence of another compound take on 1,000-fold greater potency.*

"This is another factor that seriously complicates the quantification of potency in the carcinogens at this state in our knowledge of the problem. (Upton, Tr. 319, emphases added)

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"Trichloroethylene in the animal system behaves as a weak carcinogen. I stress that we have insufficient evidence to arrive at confidence estimates of the relative potency in humans, particularly since we are likely to be dealing with combinations of agents. So I think the animal data we have provides scanty basis on which to make risk estimates, quantitative risk estimates in man. (Upton, Tr. 337)

Dr. Robert Hoover (NCI) pointed out complications even in extrapolating from one group of humans to another:

"I think that you should attempt to quantify risk in any kind of study you do, whether it is animal or human. The two of us up here are basically counters, and we believe that you do not know anything unless you can measure it. So I think that in a total assessment you should attempt to measure a risk associated with exposure to specific substances for a specific duration of time. And that is useful information in trying to prevent disease.

"I think that attempting to use that information to rank carcinogens as to their potency would be to ignore the substantial amount of human evidence of variability by host factor, and other environmental exposures that we have referred to before.

"DES is not a very potent carcinogen for the vagina of the menopausal women who take it. In fact, I do not know of any association at all. Based on that you would call it a very nonpotent carcinogen. It is an extremely potent vaginal carcinogen for the fetus.

"Asbestos in nonsmokers, or uranium mining in non-smokers is associated with some hazard, but probably if you get accurate measures of it, not—in relative terms, in epidemiologic relative terms, not high. You would never suspect the 90-fold hazard associated with a smoker working in the asbestos industry.

"So I think that you should attempt to measure risks and hazards. You should attempt to relate them to specific exposures and complexes of exposures in humans, because that will be vital to your attempts to prevent disease. But I think to rely on one study in one population with all its incumbent host and other environmental characteristics to rank an agent in a potency scale would be to ignore everything we know from science." (Hoover, Tr. 805–806, emphases added)

Dr. Irving Selikoff (Mount Sinai School of Medicine) also pointed out how the example of asbestos points up the unreliability of quantitative extrapolations from animals to humans:

". . . let me tell you my unhappy experience. I suspect we learn at least as much from our failures as we do from our successes. For years I was told that asbestos was not a powerful carcinogen, because the animals did not show cancer with it. Animal studies began with asbestos in 1930, and the first cancers were produced only in 1962, Dr. Wagner.

"I began asbestos research around 1951, and for the first ten years of my asbestos life, I was studying alveolar capillary block syndrome, and physiological changes, because I did not—I was told that there was no particular cancer hazard on the basis of animal studies, and it was not a potent carcinogen. Well, obviously I was wrong. Maybe the animals did not smoke and did not live in the rest of the environment in which humans live, neither the workplace nor at home, nor whatever. So *that potency has to do with many things. Also, what might be potent in one set of circumstances or in one animal, might not be potent in another. And there is no way to predict.* Sometimes you cannot even extrapolate from mouse to rat, and what might be potent in a rat may not be in a mouse, and what may not be potent in a guinea pig may be very potent in a dog. For example, you know very well that beta-naphthylamine, in order to get a bladder cancer acknowledged, we had to study dogs, and I think some of the best studies in the world were done by du Pont with regard to the dog studies and bladder carcinogens. So it is very difficult to extrapolate on the basis of current knowledge with regard to potency, yet there is difference in potency.

"But even then, look at what happens with human beings. You can take a very weak carcinogen like cigarette smoking. You know, cigarette smoke is a very weak carcinogen. In humans you have to give it to them for 30 years, 20 times a day before they will get cancer, and even then not all of them will get it. It is a weak carcinogen, and yet it can take a tremendous toll.

"This year in the United States we expect 100,000 deaths of cancer in considerable part due to cigarette smoking. So the question of potency is one unfortunately that we cannot extrapolate from knowledge that we currently have.

"Also, I have another bad experience, let me confess. I was in Houston, Texas, in 1970 when Dr. Viola reported Zymbal cell tumors of the rat ear with vinyl chloride. And I walked away, and I said gosh, another Zymbal cell tumor agent. Isn't it nice that human beings do not have any Zymbal cells in their external ear? And it was not until 1974 that nature hit me in the face with the angiosarcomas of the liver, and with perhaps other tumors. So that potency of one type in one animal really does not help guide us. And yet there is a difference in potency. Perhaps 10 or 15 years from now when we have better basic information, when we know something about mechanism, when we know something about pathogenesis, we will be able to sort this out better than we can now." (Selikoff, Tr. 1753–1755)

Dr. John Berg (Colorado Regional Cancer Center) made a related point:

"I am not quite sure what potency means. The best I can understand, something with

low potency would be a material that only had, say, a low level of contaminants by a strong carcinogen, or that was metabolized in the body only in a small fraction to an active carcinogen. And, of course, if we are talking, as some people have said in the cyclamate story, about the contaminants in part, then we are getting back to basically a strong carcinogen. If we are talking about metabolic changes, we are talking about what individuals do. And the implication might well be that what was a low potency for one individual would be high potency for another. But I cannot visualize a material that in some way was a direct but weak carcinogen. To my mind it does not make biologic sense." (Berg, Tr. 1627)

Dr. Marvin Schneiderman (NCI) discussed both scaling questions and differing susceptibilities:

"We have some information in the animal studies, generally at substantially higher doses, and that means that we have to then do some, as it were, modeling. You have to create a mathematical model that is consistent with the biology, and the mathematician and the biologist have to work closely together to see that such a model is created.

"Data which are fit by a whole series of models at medium and high doses, when one looks at the extrapolations from the different models, can give you rather different—substantially different—estimates of risk down at the rather low dose levels. So one of your problems is the model that you assume, and how you use it.

"Another problem is that we are trying to extrapolate from, in general, inbred, highly inbred animals, the mouse or the rat or something of that sort, to an outbred animal, man, with a much wider range of susceptibilities. So that while the animal data—what may happen when you look at the human exposures is that humans at some very low levels might be very susceptible, whereas in this rather inbred strain of mouse you don't have individuals so susceptible.

"Let me give you a rather obvious example. There was a blond-haired, blue-eyed lady here earlier today. She is at much greater risk of skin cancer than would be a dark-haired, dark-skinned person. So we have this enormous range in humans, but within an inbred strain of animal, you don't get this wide range.

"Secondly, the animal lifespan is very much shorter than man's, maybe of the order of 1/35th. Third, the animal metabolism rates are usually very much higher than that of man. There is the further difficulty in these kinds of extrapolations that in general we work with very small numbers of animals compared to the kind of population we want to extrapolate to. If we do an experiment with 1,000 mice, which is an enormous experiment, we may want to be extrapolating this kind of information to 100 million humans. I don't know how many mice that takes to equal one man, or how many men equals one mouse in that, but is it of the order of 1,000 or 10,000, or something like that, or is it 100,000? So we are using the mouse as a surrogate for an enormous number of people.

"So all these difficulties come into making the extrapolations down to low doses, and from one species to another." (Schneiderman, Tr. 798–798)

Dr. Matthew Meselson (Harvard Univ.) and Dr. Joyce McCann (Univ. of Calif.) discussed the difficulty in comparing "potencies" of chemicals in different species, and suggested that when properly analyzed the data suggested inter-species variations by up to a factor of at least 100. Dr. McCann discussed this latter point in her oral testimony:

"I suspect that there is a wide range of carcinogenic potencies in people. People I do not think are that different from rodents. The problem that we are confronted with is are they ordered in the same way that they are ordered in this chart? This is rodent data. And that is where enormous uncertainties creep in. We have limited information on that score. One of the primary sources of information about potency in rodents compared to potency in people is the work that Dr. Meselson did that was discussed some this morning, trying to estimate the exposure of people to chemicals that have been associated with human cancer, and to compare the carcinogenic potency of those chemicals in people with the potency from the animal cancer tests. And as he indicated this morning, considering there is a million to ten million-fold range of possibilities for answers from that kind of exercise, the fact that he came up with differences that were 100-fold or even less in some cases I think is enormously significant." (McCann, Tr. 1598–1599)

Dr. Meselson pointed out that quantitative risk estimates could be useful for certain purposes even granting uncertainties by up to a factor of 100:

"You see, if there is only a difference of even 100, that sounds enormous to some for species differences. It suggests interesting metabolic differences perhaps between the two species; an area for fruitful research, all that, so you will concentrate on it. On the other hand, for practical purposes, maybe that factor of 100 even, which is a big factor now, is not so bad because if we could even reliably divide chemicals into, say, four categories—carcinogenic chemicals—very strong, strong, medium and weak—and be really sure of that, strength categories as applied to man, we would be a big step beyond where we are today. If we could divide them into 10 shades, 10 categories, that would be tremendous." (Meselson, Tr. 1541)

Dr. Richard Bates (NIEHS: FDA) made another statement about factors complicating quantitative assessments:

"When I put on my scientific hat, I have to admit that our basis for doing this is very uncertain at this point. There are just a lot of quantitative uncertainties here: the problem of differences in the ratios of different kinds of metabolites among species; the rates of metabolism among species or among human individuals with differences in genetic background, and differences in susceptibility of individuals across this wide range of genetics in the human population compared to the limited genetics in the animal strains; the exposure of people to probably quite a few carcinogenic and cocarcinogenic chemicals, and the background of their environment against which you are adding this one that you are trying to evaluate at this particular time, in contrast to animal experiments that are designed to try to minimize this. All of this puts this matter of potency on a very uncertain scientific basis.

"Now, that is not to say, and I would certainly agree that if you conducted an experiment on 20 different carcinogens in one strain of mouse or rat under set experimental conditions, you will certainly see a wide range of potency under those given experimental circumstances. (Bates, Tr. 610)

Finally, Dr. Samuel Epstein (Univ. of Ill.) commented on interspecies extrapolation as follows:

"Clearly, when you have dose-response situations, and most of our dose-response data does, in fact, come from animals, when you have dose-response situations it is possible to develop extrapolations within that particular species, and to develop interesting concepts of so-called risk estimates.

"However, when you try to extrapolate and try to develop risk estimates from one species to another, this is a frightfully difficult game. In other words, going from the mouse to the rat is a frightfully difficult game. When you go from the mouse to the human, when the mouse, you have data dealing with exposures to mice under carefully controlled laboratory circumstances with carcinogen A in a controlled environment—to go from that to man, you are faced with the following problems. A, in man you do not know—even if you assume that in principle there was a comparable sensitivity at any one point, you do not know the relative shape of the dose-response curves firstly. And also, man unlike mouse is at far greater risk from exposure to any individual carcinogen because exposure to any individual carcinogen represents an incremental insult over that of a wide range of other chemical carcinogens to which he or she are concomitantly exposed. So therefore, it becomes a terribly difficult matter to say I am taking dose-response data from animals to go to humans. (Epstein, Tr. 1229–1230)

Among industry witnesses, Dr. Paul Kotin (Johns-Manville) discussed factors affecting response in animal systems at some length:

"1. *The Cancer-Producing Potency Of Chemical Carcinogens Can Be Profoundly Altered By Modifying The Host, The Complexity Of The Environment, And The Physical Properties Of The Chemical Agent*

"Changes can be accomplished through (a) pretreatment with chemical agents (both carcinogenic and noncarcinogenic) which can either stimulate or depress drug-metabolizing enzyme systems; (b) diet modification; (c) hormonal modification by endocrine gland removal or artificial administration of hormones; (d) varying population size (density) in laboratory animal cages (34). Significant induced as well as spontaneous differences exist in the human response to carcinogens. When, for example, the site and

patterns of cancer occurrence in the nonsomoker and smoker or the alcohol user and nonuser are compared, the "shifting" levels of cancer induction bespeak a response to carcinogens that is dependent upon achieving a level of interaction (threshold) that is not fixed, but quite liable to change.

"Spontaneous or physiologic variations, still cryptic as to mechanism, are routinely observed in clinical as well as experimental settings. This individual variability is at the suprathreshold level and is essentially irrelevant to the regulatory process.

"The concept that one molecule of a carcinogen interacting with one intracellular macromolecule will result in a mandatory nonthreshold response, inevitably resulting in cancer development, precludes both naturally occurring and induced modifications of response to carcinogens. The multiplicity of cofactors both exogenous and endogenous critical to the response to a carcinogen and the development of cancer is reflected in greater qualitative and quantitative variations in the human response to carcinogens than all other environmental agents. The paucity of knowledge of the mechanisms of cell initiation and their progression to clinical cancer has generated a mystique, as a frequent substitute for data, when interpreting diverse pathological expressions of the group of diseases designated cancer. For example, each organ or organ system can develop an array of different types of cancer, often with important differences in natural history, in response to exogenous carcinogens. As shown in Table I, a variety of cancers develop from environmental agents, and one wonders whether the various histological patterns and types (a) reflect qualitative or quantitative differences in intra-cellular genetic events; (b) are manifestations of response at the tissue level; or (c) are expressions of host factors operating at the systemic level. Critical to the above is the continuing opportunity for carcinogen-exposed tissue to express any one of its multipotential capabilities. While the factors concerned with the ultimate path are for the most part unknown, clearly dose and its corollary threshold can be shown to be involved." (Kotin, S. 23–24)

Dr. Kotin also discussed a number of factors which would need to be studied in evaluating experimental results in carcinogenesis (Kotin, Tr. 8653–8680).

Dr. Robert Scala (Exxon) emphasized uncertainties in both qualitative and quantitative extrapolation resulting from these factors:

"Carcinogenic potential as shown by animal testing, and actual carcinogenic risk in humans, are clearly different. Carcinogenic potential can be demonstrated with some rigor by studies of a chemical in animals. The results are, of course, subject to such influences as dose, duration, route of administration, pretreatment, and others I have already mentioned. Carcinogenic risk assessment in humans, however, requires far more scientific judgment, not only taking into account the amount and quality of the experimental data but also to correlate it with and extrapolate it to realistic circumstances of human exposure." (Scala, S. 18)

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"Eckardt's third type are biologically-trained, biologically-oriented individuals who attempt to make extrapolations from animals to man with a proper understanding of the limitations and with a high degree of intellectual and scientific sophistication and honesty. These individuals take into account questions of mechanism of action, whether or not biochemical activation is necessary, what metabolic pathways may be involved, whether or not host factors may be protective, the possibility of initiation-promotion phenomena, and finally the important issue of metabolic overload. Careful extrapolation from animal data to human risk must and can be done, on the basis of which we can set realistic and practical human exposure levels that will provide sound public protection without overreacting by establishing technologically and economically infeasible regulatory requirements. It is this type of sophisticated scientific evaluation that must be incorporated into the revision of the OSHA proposal if it is to be implemented successfully." (Scala, S. 21–22)

Dr. Francis J. C. Roe (AIHC) discussed three assumptions necessary in extrapolating carcinogenic risks to humans, and suggested that uncertainties by several orders of magnitude may result:

"The main difficulties for the future, however, lie in situations where human data are inadequate, or even, non-existent. In these situations the extent of risk to man can only be judged on the basis of the results of laboratory tests, including long-term tests on animals. In making the jump from animals to man, 3 basic assumptions have to be made: *Firstly,* we need to assume that an agent which reduces life expectation by a certain percentage in an animal will reduce life expectation by the same percentage in man and not by the same actual length of time. *Secondly,* we need to assume that man is equally sensitive to the carcinogenic effects of an agent as the laboratory species in which tests have been carried out. *Thirdly,* we need to assume that there is a linear relationship between exposure and loss of life expectation. The *first* of these assumptions is generally well borne out for known carcinogens for which there exist both human and animal data. The *second* assumption is probably also generally reasonable. However, interstrain and interspecies differences in susceptibility to carcinogens are known to exist and are sometimes so marked that an agent which gives positive results in one strain or species at a well tolerated dose-level may be without detectable carcinogenic effect in another species even at maximum tolerated doses. Where the animals used for tests have built into them genetically-determined high susceptibility to the development of certain tumours, or where they carry tumour viruses which increase the risk of tumour development (see 3.3.3), it is highly likely that the animals used are *more* susceptible, possibly by several orders of magnitude, than man. On the other hand, the possibility that man is more susceptible than any of the usually used species of laboratory animal can never be excluded. The *third* assumption is, as we have already argued (see 7, 16), conservative." (Roe, S. 84A–84B)

A number of other industry witnesses and commentors emphasized the importance of such factors as metabolism, pharmacokinetics, and DNA repair, and urged OSHA to take account of these factors in evaluating experiments. For reasons elaborated in the Sections titled *Testing at High Doses* and *Metabolism,* OSHA concludes that such factors are not of major importance in the *qualitative* extrapolation of experimental results to predict the existence of a risk to exposed workers. OSHA agrees that such factors would be important if detailed quantitative estimates of risk were to be made for the purpose of risk-benefit comparisons. However, the testimony and exhibits quoted above indicate that (a) for most carcinogens information on comparative metabolism and pharmacokinetics is not presently available, and is unlikely to become available without direct experimentation in man; (b) our understanding of these phenomena is insufficient to make confident predictions in the absence of precise data. Hence the primary significance of this testimony is that *metabolic and pharmacokinetic differences add enormously to the difficulties and uncertainties involved in quantitative extrapolation.* Other factors discussed in the testimony quoted above, particularly inter-individual variations and interactions with environmental and host factors, also contribute greatly to these difficulties and uncertainties. In fact, some of these factors also lead to substantial uncertainties even in ranking chemicals relative to each other in the degree of risk they pose to exposed humans.

6. *The Role Played by Quantitative Risk Estimation in the Regulatory Process*

Representatives of several federal agencies discussed the role played by quantitative risk estimation in regulatory activities that fell within their purview. EPA provided the following description of its procedures in its official comments:

"Since carcinogens differ radically in potency, EPA has taken the view that quantification has a significant role to play in the regulatory process. Thus, section 3.5.3 of EPA's Interim Cancer Assessment Guidelines calls for estimates of cancer risk utilizing a variety of risk extrapolation models. . . ." (41 Fed. Reg. 21405 (1976)). Risk estimates are

performed by the Agency's Carcinogen Assessment Group ("CAG"). In providing these estimates, CAG has been assiduous in pointing out that cancer risk quantification is at the frontiers of science and that the results must be regarded as crude because of the great number of uncertainties involved in the process. Accordingly, the Agency has been advised that these estimates cannot be regarded as much more than "ball park" estimates. Nevertheless, the process has been a useful one, in that it has afforded us some measure, however imprecise, of the magnitude of the cancer risk in question. We believe that a quantitative risk assessment can be an important factor in determining whether to regulate a substance or what priority it should be given as well as how much to regulate the substance." (EPA, S. 10–11) (footnote omitted)

EPA referred in these comments to its Interim Cancer Assessment Guidelines:

"When an agent is judged to be a potential human carcinogen, estimates should be made of its possible impact on public health at current and anticipated levels of exposure. The available techniques for assessing the magnitude of cancer risk to human populations on the basis of animal data only are very crude due to uncertainties in the extrapolation of dose-response data to very low dose levels and also because of differences in levels of susceptibility of animals and humans. Hence, the risk estimates should be regarded only as rough indications of effect. Where appropriate, a range of estimates should be given on the basis of several modes of extrapolation." (41 FR 21405, Section 2.0)

EPA procedures were described further by Mr. Steven Jellinek, Assistant Administrator for Toxic Substances, and Dr. Roy Albert, Chairman of the Carcinogen Assessment Group:

"The second question of how much cancer the agent is likely to cause is answered by use of various mathematical extrapolation models applied to the animal or epidemiological results together with estimates of the levels of exposure to the agent to the extent that such estimates can be made. These quantitative estimates are regarded as crude and offered only to give rough estimates of the magnitude of the public health problem. Such estimates may be of use in setting regulatory priorities or in determining levels of feasible control." (Albert, S. 2)

* * * * *

"EPA uses a two-step decision-making process to regulate potential carcinogens. The first decision faced is whether a particular substance poses a cancer risk. The second decision is what regulatory action, if any, should be taken to reduce the risk. The two decisions are reached separately.

"Once EPA has determined that a substance being evaluated does pose a carcinogenic risk, EPA proceeds to independent analyses of the magnitude of the risk posed by the substance and, where the law permits us to do so, the socio-economic impacts of regulating the substance. Both analyses are completed before the Agency reaches a regulatory decision. The magnitude of the risk plays a significant role in EPA's regulatory process, entering into the decision whether to regulate a substance, what priority we give to regulation of the substance, and what type of regulatory action (if any) we should take." (Jellinek, S. 2)

In oral testimony, Mr. Jellinek and Dr. Albert amplified these statements to some extent. Specifically, they stated that EPA has been conducting quantitative risk assessments where possible prior to taking regulatory action since 1976 (Tr. 2289), and that it uses the linear non-threshold dose-response model as well as other extrapolation models and displays the results of each (Tr. 2289–2291). In some cases quantitative risk assessments have not been possible (Tr. 2294).

Mr. Jellinek emphasized that some statutes administered by EPA require risk-benefit balancing, whereas others specify technology-based controls, and that the role of risk assessment is different in the two cases (Tr. 2323). Mr. Jellinek emphasized the uncertainties involved in risk assessment in response to a question about risk-benefit analysis:

"Well, I think that it really depends upon what someone thinks it means when they say a risk-benefit analysis. I think if you are talking about quantifying risks and benefits in commensurable units, I think that is extremely difficult, and I frankly do not think it can be done. If you are talking about trying to get as good an idea quantitatively and otherwise of what the risk is, and as good an idea quantitatively or otherwise of what the benefit is, and then exercising your thus informed judgment to make a decision, that not only can be done but it has been done and it has got to be done or else we are not going to make any decisions." (Jellinek, Tr. 2322)

Dr. Albert made a similar comment in response to a question as to whether he felt comfortable when quantitative risk estimation is used in risk benefit analysis:

"Provided it is used with the understanding of the limitations, which I think are probably not any greater than the limitations associated with socioeconomic impact assessments. Those have a great deal of uncertainties attached to them.

"In point of fact, the Air Office in the EPA is using the quantitative risk assessment for the purpose of making priority judgments as to which agents it is going to be looking at, which carcinogens." (Albert, Tr. 2389)

In sum, EPA has determined that quantitative risk estimation is a constructive element in both the priorities-setting process and as an element in the setting of standards, recognizing the limitations involved.

Mr. S. John Byington, Chairman of the Consumer Product Safety Commission, stated in response to questions that the Commission does not differentiate between carcinogens for regulatory purposes, and uses quantitative risk estimation only in terms of setting priorities. (Tr. 2089, 2095)

Dr. Donald Kennedy (Commissioner, FDA) limited his comments on this issue primarily to suggestions that OSHA should use quantitative risk assessment as one component of decision-making (S. 11). He introduced one FDA rulemaking—the proposed rule to revoke the interim food additive regulation for saccharin and its salts (42 FR 19996). In that document FDA made estimates of potential risks to humans consuming saccharin, these estimates being derived both from animal tests and epidemiological data (p. 20002). FDA then used these estimates only in a general way to support its proposed rule:

"The Food and Drug Administration thus considers the animal data and the human epidemiological data on saccharin to be compatible. The estimated excess risk to the individual of developing bladder cancer from lifetime use of, e.g., 150 milligrams of saccharin per day, is believed to be somewhere between zero and 4 per 10,000. The estimated population risk in the United States, assuming such use by each individual, is somewhere between zero and 1,200 cases per year.

"Although the risk from consumption of saccharin is small compared to that of other health hazards, e.g., cigarette smoking, saccharin is only one of a potentially large number of hazards present in our environment. The Commissioner believes that reduction of prolonged, general exposure to a number of weakly carcinogenic substances in our environment as they are discovered may be essential to reduce the total incidence of cancer." (42 FR 20002)

Dr. Richard Bates (NIEHS; FDA) discussed this assessment and stated:

"Yes, but it was done just as kind of a crude handle of where we might be, and then the conclusion was that we get rid of exposure. We reduced it to the lowest feasible level, which is zero in the case of saccharin." (Tr. 684)

In response to questions, Dr. Kennedy indicated his opinion that quantitative risk assessments should be used for priority-setting and for public education, but not for risk-benefit analysis as a component of regulatory decision-making:

"I think you are really asking whether the second [assessment or extrapolation of risks for humans] I am saying that it should be done because there are very often important purposes affiliated with it; perhaps setting of agency priorities, perhaps public education about a hazard, various things, but that seldom is the precise magnitude of an assessed or extrapolated risk a critical

feature in Stage Three, namely, regulatory decision-making." (Kennedy, Tr. 514)

Dr. M. Adrian Gross (FDA) stated in response to questions that he was familiar with only one proposed regulation in which FDA had used quantitative estimation of risk for regulatory purposes (Tr. 1940). In that proposed regulation, applying to residues in food-producing animals (42 FR 10477), Dr. Gross stated that the Mantel-Bryan extrapolation procedure was not used to assess human risk, and indeed he emphasized that "one cannot use the Mantel-Bryan procedure or other procedures like it to assess human risk at all" (Tr. 1938).

The representatives from NIOSH, Mr. Baier, Dr. Groth, and Dr. Yodaiken, stated that it was NIOSH's position that the potency of carcinogens has very little weight and should not be considered in evaluating carcinogens (NIOSH, Tr. 3063–3067, 3112–3113). It is not used by NIOSH even for evaluating priorities:

"In animal experiments there is a difference, of course, in dose response in the same species to different chemicals. However, unless we have human data we really cannot evaluate these comparisons between chemicals in humans unless we have this data. We have to assume that these chemicals have the same or equal potency in humans until some other data is acquired." (Groth, Tr. 3064–3065)

Mr. Richard Peto (Oxford Univ.) described the procedure for regulating carcinogens in the United Kingdom by the Carcinogenicity Committee of the Department of Health and Social Security, of which he was a member (Tr. 2568–2570). He explained that "potency" of carcinogens was considered in this process only in an informal way, and that modeling techniques for risk assessments are not used:

"No. I think that they are not of great value. The formal modeling I think is not of great value. I think that many of the models currently employed are misleading. They give a misleading impression of safety sometimes. And I think that, their logical basis is, in some cases, rather unsound, and that many of them have implicitly the assumption that there is no equivalent background, and that this is very dangerous.

"So I think that we do not use models, and I am glad we do not. I am the only statistician on this committee." (Peto, Tr. 2570)

In summary, EPA is the only one of the five agencies whose procedures were discussed in the Record which makes quantitative estimates of risk on a regular basis in determining the degree of regulation. The Agency believes:

". . . that a quantitative risk assessment can be an important factor in determining whether to regulate a substance or what priority it should be given as well as how much to regulate the substance." (EPA, S. 11)

This belief is qualified by the EPA's recognition of the uncertainties involved in quantitative risk estimation, and in fact its decisions on "how much to regulate the substance" are not based on mathematical comparisons of risks and benefits, even where EPA (unlike OSHA) is required by statute to balance risk and benefits. As Mr. Jellinek explained (Tr. 2322), EPA's procedure is to get "as good an idea quantitatively of what the risk is," and then to exercise its "thus informed judgment to make a decision." Other agencies concur as to the usefulness of risk assessments for priorities setting.

7. Specific Proposals for Making Low-Dose Risk Estimates and for Using Them in Regulation

As noted earlier, a number of witnesses and participants recommended that OSHA should use quantitative risk estimates in the standards setting process. Section X1.B.7 contains a detailed discussion of these proposals and their methodological deficiencies. This section is limited to a discussion of the implications of large uncertainties in health estimates for the usefulness of such analyses. Only one fully specified procedure was proposed by any participant. Dr. Richard Wilson (Harvard Univ.) proposed a procedure by which the concept of "feasibility" of control should be replaced by a risk-benefit analysis. In brief, Wilson proposed that a "conservative" estimate of risks at low doses should be derived by application of the linear non-threshold model to either human or animal data, and that a specific level of exposure should be regarded as acceptable if the calculated risk were less than 10^{-5} per year (i.e., risk less than 1 cancer per 100,000 workers per year). At higher risk levels the number of lives likely to be saved by specific measures to reduce exposure should be calculated, and control measures should be regarded as justified if their estimated cost does not exceed $1 million per life saved. Additional details of the proposed procedure, including methods for extrapolating from partial lifetime exposure data, were given in Dr. Wilson's statement.

There are a number of methodological problems with Dr. Wilson's proposal which would make it unreasonable, if not arbitrary, for OSHA to adopt it. This section will deal only with the dependence of this procedure on reliable assessments of risk. His procedure would require the assumption that the estimates of risk generated by it are sufficiently accurate to balance against estimates of control costs. As shown in the preceding two sections, enormous uncertainties are introduced into extrapolations from animals to man by such factors as differences in metabolism, pharmacokinetics, and scaling factors. Even Dr. Wilson, who minimized such differences in his testimony, acknowledged the possibility of errors by up to a factor of 200 from scaling factors alone (Hearing Exhibit 51). Even where epidemiological data in humans are available as the basis for extrapolation, substantial uncertainties may be introduced by different interpretations of the existing data, selection of "best" data from which to extrapolate, and extrapolation from partial-lifetime to full-lifetime risks (see Nisbet (Post-hearing Comments (Hearing Exhibit 224e), and Wilson, Response to Nisbet (Hearing Exhibit 251B)). Finally, Wilson's use of a linear, non-threshold extrapolation model was rejected as too conservative by many industry witnesses, whereas in fact it was not as conservative as other models in one respect: it did not incorporate a statistical upper confidence limit. On the basis of these and other limitations discussed in the preceding sections, and section X1, OSHA concludes that neither Wilson's procedure nor any other comparative risk framework that could be devised would be reliable within a factor of 100 or more, usually much more. Although estimates obtained by the use of this procedure may help OSHA to make "informed judgments", clearly it is not useful in practice to set standards.

The only other specific recommendation for a risk assessment procedure presented in the record is that of the Scientific Committee of The Food Safety Council. After extensive discussion of alternative methods of risk assessment, they made the following recommendation:

"7. The choice of mathematical procedures for low dose extrapolation has no firm biological basis and must to some extent be arbitrary. But the chief alternative to low dose extrapolation is the setting of zero tolerances for any substance that is harmful at sufficiently high doses, i.e. nearly everything. But zero tolerances are not reasonable alternatives for many agents which have clear benefits for man. Thus, risk assessment is unavoidable and must, implicitly or explicitly, involve a balancing of risk and benefit. We recommend the gamma multi-hit model for estimating responses at low dose levels and the virtually safe dose, corresponding to an arbitrarily small level of risk, chosen for each agent by decision-making authorities after consideration of the

risk and benefits involved." (Food Safety Council 1978, p. 119; Hearing Exhibit 227)

There are serious questions about whether this proposed procedure for food additives would be compatible with OSHA's statutory mandate to "assure" protection of workers' health "to the extent feasible." Apart from this, the procedure would utilize the gamma multi-hit extrapolation model, which as shown above has received no support from the scientific community.

Dr. Joyce McCann (Univ. of California) discussed what she believed was the proper role of risk assessment in the regulatory process in her written statement. While recognizing that estimates of carcinogenic potency may be uncertain by one or two orders of magnitude, she concluded that they may still be useful as a "check on the reasonableness of a standard set according to feasibility":

"Risk estimates can be wrong by an order of magnitude, or even more, and still be useful as rough estimates in determining if the lowest feasible level is compatible with acceptable risk." (McCann, S. 3)

In oral testimony she expanded upon this concept:

"Well, certainly for prioritizing chemicals, potency can have great value. I mean, when one is faced with a very long list and you have to decide where to start, I think potency and human exposures should play a very useful role in ordering priorities. And I suspect that is how they will end up being used.

"But in addition, I would also like to see an awareness of an upper limit exposure based on a risk-assessment calculation after lowest feasible levels are set, a check." (McCann, Tr. 1602)

However, she cautioned that:

"Although risk estimates can be useful within the context of the lowest feasible level approach, they should not be used to set exposure levels higher than the lowest levels feasible." (McCann, S. 4)

This suggestion is compatible with the reservations expressed above about the use of uncertain estimates in making precise cost-benefit comparisons. Dr. McCann's suggestion appears to be to use risk assessments to check whether the rough estimates of risk, at the lowest feasible level, are not too high to be "acceptable". If they are, then action by Congress, EPA under the Toxic Substances Control Act, or other actions may be appropriate.

A similar suggestion was made by Mr. Jellinek and Dr. Albert (EPA):

"Second, we encourage OSHA to include risk estimation in its regulatory process. While cancer risk estimation is an imprecise endeavor involving many uncertainties, such estimation does succeed in providing some measure of the magnitude of risk posed by a substance. Such estimation should be used, in some instances, to determine whether to regulate. If a substance is believed to be a carcinogen but is a weak carcinogen to which few persons are exposed, the best regulatory course might be to defer any regulation in favor of concentrating limited resources on higher toxicity, higher exposure substances. OSHA's proposal does not appear to permit the agency to adopt this course. We believe that OSHA also should use estimation of risk to help establish priorities and to help determine "feasibility" of various levels of control. The greater the degree of risk posed by a substance, the tighter the control should be of that substance." (Jellinek, S. 5–6, emphasis added)

* * * * *

"Finally, a comment on the matter of quantitation of cancer risks. The extrapolation of cancer risks to very low levels of exposure is undoubtedly more useful to EPA than OSHA. In the general environment, exposure to carcinogens can commonly be very low and involve large populations. In the occupational setting the potential for exposure is always high. Nevertheless, because carcinogens can vary in potency by as much as a million fold, OSHA should strongly consider using quantitative risk assessment to the extent possible for prioritization of chemicals and as a factor in judging feasibility of regulatory control. (Albert, S. 6)

8. *Performing Risk Calculations for Individual Substances*

A number of risk calculations for specific chemicals were introduced into the record in statements and exhibits (see, for example, the statements of Drs. Wilson, Hoel, and exhibits thereto). For two chemicals, vinyl chloride and saccharin, a range of estimates derived by different methods was presented; these estimates provide a good illustration of the strengths and weaknesses of the various techniques.

(a) *The example of vinyl chloride.*— For comparative purposes, all the risk estimates presented in the record are converted here to lifetime risks at an exposure level of 1 ppm. Seventeen such estimates are presented in the first table below, with the method of extrapolation and the source of data. These estimates span an enormous range; even if the "threshold" postulated by Claus is discounted, estimates of risk at 1 ppm range from 10^{-8} to less than 10^{-2}—more than a million-fold variation. The variation arises from several sources: use of different source data, different extrapolation models, and in some cases calculation of upper confidence limits. However, other variables, such as scaling factors, interspecific differences in susceptibility, and prenatal exposures, were not considered by the cited authors, so that the full range of possible variation is still not represented.

(b) *The example of saccharin.* The second table below was compiled by the Committee for a Study on Saccharin and Food Safety Policy (NAS 1978). It shows a range of variation of more than 5 million-fold in estimates of human risk, although all the estimates were derived from the same set of experimental data on rats. Other estimates of saccharin risks included in the record, including those by FDA (41 FR 20002), Wilson (S. 41, 73), and OTA (1977), fall within this range. However, at least one published estimate of risks posed by saccharin lies outside this range. Miller *et al.* (1978), extrapolating from human epidemiological data, estimated that lifetime use of saccharin by the U.S. population might result in as many as 48,000 cases of bladder cancer per year, equivalent to a lifetime risk of 15,000 cases per million exposed. Thus the possible range of risk estimates for this chemical is greater than 10 million-fold.

(c) *General conclusions.* For each of these two chemicals, estimates of possible risks at exposure levels which are currently permitted vary over ranges of 1–10 million or even more. Few chemicals have been more thoroughly studied than vinyl chloride, which is one of only half a dozen chemicals for which numerical data on risk derived from human studies are available (NAS, 1975a). Yet even in this case it is not possible to state whether the cost of averting one occupationally-related cancer is greater than $100 million (Wilson S. 53), or as little as $100,000. Clearly it would be not only unjustifiable but irresponsible for OSHA to use any such single point estimate as part of a simple summary cost/benefit statement (and guide to standard setting) as proposed by Wilson. In the face of uncertainties of many orders of magnitude in anticipated cancer risks, a fair analysis of available facts must alert the decision-maker to the wide range in the level of cancer risk which may reasonably be foreseen under alternative interpretations of available data.

Single-point estimates of risk are inappropriate. In view of the health-protective mandate of the OSHA Act, it is particularly necessary for OSHA in considering standards for carcinogens to take appropriate notice of the many types of circumstances which can lead to much greater human risks than might be inferred from simple "best estimate" calculations based on standard linear no-threshold interpolation. Among these circumstances are:

• *Difference in species sensitivity.* As previously noted (see comments of Dr.

Trump, Tr. 1974–5, quoted above), the potency of beta-naphthylamine in inducing bladder cancer in animal systems would, if directly used in the absence of human data, have led to a understatement of the actual human cancer hazard of this material. Available data for quantitatively comparing cancer risks for man and other species are so few at present that 1) even if available data from the most apparently sensitive animal species is used for cancer risk assessment on a particular substance and 2) even if a conservative scaling factor is used for the animal to human dose conversion, there should generally be considered to be an appreciable chance that the human risk might greatly exceed the calculated animal risk due to intrinsic differences in species sensitivity. Absent other information, it would not be unreasonable in presenting risk estimates to allow for a possible uncertainty of 100-fold or more from this factor alone.

• *Differences in individual sensitivity.* Animal carcinogenesis data usually represent the response of relatively homogeneous groups of animals. Animal colonies are often inbred, reducing genetic variation among individual animals, and there is a deliberate effort to minimize the variability in environmental exposures which might interact with the substance being tested for carcinogenicity. By contrast, it was noted repeatedly in the hearings that worker populations exposed to carcinogens can be expected to be relatively heterogeneous collections of individuals—with substantial variations in both genetic factors (influencing, *inter alia,* metabolic handling of carcinogens and the efficiency of repair of pre-carcinogenic DNA lesions) and potentially interacting environmental factors (e.g., the difference in cancer risk between smoking and non-smoking asbestos workers). Even if the basic form of the relationship between dose and cancer risk within each individual is linear, if there are substantial differences between individuals in susceptibility (slope of the dose/cancer risk relationship) within an exposed population, the number of cancers produced in a population by low doses of carcinogen will generally *exceed* the number which would be expected from a simple linear interpolation from high dose observations. The degree to which a simple linear interpolation may understate the true risk due to such individual variability is not yet known for any specific carcinogen.

It is recognized that there may be factors which would result in a linear extrapolation being an over-estimate of the risk, but the Secretary must be especially concerned with the possibilities of high worker risk and err on the side of caution (IUD v. Hodgson). OSHA will not, in general, have any reliable body of data for predicting the likely degree of individual human variability in sensitivity to specific chemicals to be regulated. However, in view of the testimony that appreciable inter-individual variability has been observed in drug metabolism and carcinogen binding to DNA (e.g. the work of Hammer and Sjoqvist, 1967, finding a ten-fold variation among twenty patients in the half-time for disappearance of tricyclic antidepressants from plasma, and the work of Harris and Trump, 1976, finding a 70-fold variation amoung 37 patients in the amount of the carcinogen benzo(a)pyrene bound to DNA in human bronchi cultured under similar conditions (Harris, S. 3–4)), there may often be an uncertainty of 10-fold or more due to this factor.

• *"Plateau effects."* The original Maltoni animal experiments on the carcinogenicity of vinyl chloride at various dose levels illustrate another potential hazard of simple linear interpolation of cancer risks from high to low doses (Maltoni, 1975). The Maltoni data from experiment BTI span a very large range in dosage from 50 ppm to 10,000 ppm. By contrast, most current carcinogenesis bioassays are done for only two very high doses (a "maximally tolerated dose," and a dose estimated to be about half that). The Maltoni data for vinyl chloride exhibit a plateau in the carcinogenic response at the highest dose levels. There are relatively small differences in the yield of total tumors or angiosarcomas between the animal groups given doses from 500 to 10,000 ppm. At 500 ppm and below, there is a fall-off in tumor yield compatible with a linear dose-response relationship. If, in the case of vinyl chloride, only the two highest dose levels (6,000 and 10,000 ppm) had been tested, and a linear-dose response relationship had been assumed beginning with the point at 6,000 ppm, the risk at the 250 ppm level would have been underestimated by over 10-fold, compared to the actual results at 250 ppm. Thus, when making risk estimates from data covering a very limited range of dosage, it is quite possible that simple linear interpolation from the lowest dose which happens to be available may lead to ten-fold or greater errors if the carcinogenic response shows a plateau similar or worse than that found with vinyl chloride. This is essentially the point made in the testimony of Dr. Gehring (Dow Chemical), although Gehring presented his data in a way which obscured the fact that "metabolic overloading" in this case gave rise to a massive underestimation of risk.

• *Uncertainty in future chemical usage and worker exposure.* A final factor which may contribute substantial uncertainty to estimates of the number of cancers which may result under a given exposure standard is the future changes in the number of workers who may be subjected to exposure to the regulated substance. Clearly, if the regulated substance is used in an expanding industry, over a period of several years the number of workers at risk (and the number expected to eventually develop cancer) may rise by many-fold from the number exposed at the time the standard is promulgated. A similar expansion of the risk may occur if the regulated substance comes into wide use for new applications.

All of these considerations make it prudent to regard "best estimates" of cancer risk from simple linear interpolation of animal or human epidemiological data as potentially understating actual cancer risks by orders of magnitude.

9. *Is Mutagenic "Potency" a Useful Predictor of Carcinogenic "Potency"?*

Dr. Matthew Meselson (Harvard University) introduced a paper in which he and his colleague, K. Russell, had compared the carcinogenic "potencies" of 10 carcinogens in rodents with their mutagenic "potencies" as measured in the Ames *Salmonella* reversion test (Meselson and Russell, 1977). Both carcinogenic and mutagenic potencies were carefully defined, and the authors found a "rough . . ." correlation between the two:

> "For a variety of compounds which are both carcinogenic and mutagenic, it is found that the carcinogenic potency k in laboratory rodents is approximately equal to the mutagenic potency m in Salmonella, using definitions of k and m given in the text. An exception to this relationship is noted for a number of nitroso compounds, for which k is considerably greater than m.
>
> "It is suggested that the carcinogenic potency of a mutagenic compound for man may be roughly equal to that in rodents if the carcinogenic potencies are expressed in terms of the average normal life-spans of the respective species." (Meselson and Russell, 1977, p. 479; Exhibit 18 to Hoel Statement.)

If such a correlation can be confirmed by further measurements on specific classes of carcinogens, it might perhaps prove possible to improve predictions of potential low-dose risks to humans, avoiding some of the complexities and

uncertainties discussed in previous sections. However, at present, data are extremely limited (see Goldman, S. 20). OSHA is aware of a large-scale study in progress which would throw light on this possibility (Ames and Hooper, 1978). Pending the results of such a study it would be premature to consider its incorporation into any scheme for risk assessment.

Estimates of Lifetime Risk From Exposure to 1 ppm Vinyl Chloride

Source	Estimate of lifetime risks	Method of extrapolation	Source of data
Wilson (S. 53)	2.5×10^{-6}	Linear	Epidemiological unspecified source.
Wilson (Exh. 251 B)	5×10^{-4}	Linear	Epidemiological and Maltoni (unspecified).
Crump and Guess (1977), exhibit to Hoel statement.	2×10^{-4}	Multi-stage, upper confidence limit.	Maltoni (1975).
Guess *et al.* (1977), exhibit to Hoel statement...	2×10^{-4}	Multi-stage, upper confidence limit.	Maltoni (1975).
	1×10^{-4}	Mantel-Bryan, upper confidence limit.	Maltoni (1975).
Claus (S. 38)	0	Assumption of threshold at 10^{4} molecules per cell, calculated to occur at exposure level of 4.9 ppm.	
Nisbet (post-hearing comment, p. 6)	4×10^{-3} to 1×10^{-3}	Linear	Maltoni (1977), Table 12.
Gehring *et al.* (1978), p. 590	10^{-3}	Log-probit, extrapolation of observed dose-response curve.	Gehring *et al.* (1978), dose-response curve based on unmetabolized VC.
Hooper and Ames (1979)	Greater than 10^{-3} (rats)	Linear	Maltoni (1977), liver angiosarcomas.
	Greater than 10^{-2} (rats)	Linear	Maltoni (1977), mammary tumors.
	10^{-1} to 10^{-2} (humans)	Linear, extrapolated to humans.	Maltoni (1977).
Food Safety Council (1978)	10^{-3}	Multi-hit	Maltoni (1975).
Do	2×10^{-2}	Multi-hit, upper confidence limit.	Maltoni (1975).
Do	5×10^{-6}	Multi-stage	Maltoni (1975).
Do	8×10^{-5}	Multi-stage, upper confidence limit	Maltoni (1975).
NAS (1977), exhibit to Hoel and Rall statements, p. 794.	2×10^{-2} [a]	Multi-stage, upper confidence limit.	Maltoni (1975).

[a] Assuming breathing rate of 15 m^3/day to convert from oral intake to inhalation exposure.

Estimated Human Risks From Saccharin Ingestion of 0.12 g/Day (From NAS 1978, p. 3–72)

	Lifetime cases/million exposed	Cases per 50 million/yr
Rat dose adjusted to human dose by surface area rule:		
Method of high- to low-dose extrapolation:		
Single-hit model (Hoel, 1977)	1,200	840
Multi-stage model (with quadratic term (Hoel, 1977)	5	3.5
Multi-hit model (Scientific Committee of the Food Safety Council, 1978)	.001	0.0007
Mantel-Bryan probit model (Brown, 1978)	450	315
Rat dose adjusted to human dose by mg/kg/day equivalence:		
Method of high- to low-dose extrapolation:		
Single-hit model (Saccharin and Its Salts, 1977)	210	147
Multi-hit model (Scientific Committee of the Food Safety Council, 1978)	.001	0.0007
Mantel-Bryan probit model (Brown, 1978)	21	14.7
Rat dose adjusted to human dose by mg/kg/lifetime equivalence:		
Method of high- to low-dose extrapolation:		
Single-hit model (Brown, 1977)	5,200	3,640
Multi-hit model (Scientific Committee of the Food Safety Council, 1978)	.001	0.0007
Mantel-Bryan probit model (Brown, 1978)	4,200	2,940

D. OSHA's Conclusions

On reviewing the mass of expert testimony and conflicting opinions in the record, OSHA draws the following conclusions:

1. The "potency" of a chemical carcinogen can be defined only in relation to a specific test system and for specific experimental conditions. Although there is some correlation between the relative "potencies" of carcinogens in different test systems, there are also wide variations.

2. In the few cases where epidemiological studies provide good dose-response data in exposed humans, it is reasonable to make quantitative estimates of risks at low exposure levels. For such estimates, a linear exposure-response relationship should be assumed to represent a (single number) "best estimate" of likely risk. Data on partial-lifetime exposures should be extrapolated to predict full-lifetime risks, assuming a power-law relationship between response and elapsed time unless there is good evidence to support a different assumption for a specific carcinogen.

3. In cases where it is necessary to extrapolate from experimental data in an animal model to estimate the order of magnitude of low dose risks, the multi-stage (Armitage-Doll) model or its special case, the linear (one-hit) model have the best empirical and theoretical justification for use in making "best estimates" of likely risk at specific doses. Estimates obtained using the log-probit (Mantel-Bryan) and other models should not be presented except to show the range of potential uncertainty.

4. Pending further study and validation, time-to-event models should not be used in risk estimation.

5. While in the future it may be possible to use measurements of mutagenic potency to predict relative carcinogenic risks, at least within certain groups of carcinogens for which the correspondence may become well established, there is no adequate understanding of the correlation for such an approach to be implemented at the present time.

6. Where experimental data are available for several animal model systems, it is prudent for public health reasons to use the data from the most sensitive system as the basis for extrapolation.

7. Extrapolation from animal data to predict risks in humans introduces many additional uncertainties. These include selection of appropriate scaling factors for size, lifespan, and metabolic rate; differences in routes of exposure, duration and schedule of exposure, absorption, metabolism, and pharmacokinetics; differences in intrinsic susceptibility and repair capabilities; intra-population variation in susceptibility; and exposure to other carcinogens and intrinsic and extrinsic modifying factors. At least theoretically, these factors can affect the relative response of humans and animals by many orders of magnitude.

8. The uncertainties involved in extrapolating from high-dose animal experiments to predict low-dose risks to humans are far too large at present to justify using the estimates as the basis for quantitative risk/benefit analysis. This conclusion is well illustrated by the more than million-fold variation in the

estimates of risk derived by different authors for risks to persons exposed to vinyl chloride at the OSHA standard of 1 ppm.

9. Nevertheless, risk assessments may be useful for two purposes: (a) to predict relative risks different carcinogens when extensively studied, as the basis for establishment of priorities; (b) to estimate reductions in risks as a result of regulatory action, when adequate data exist to assess the role of the many uncertainty factors. For the latter purpose (b) single numbers for "best estimates" of expected cancer risk, derived from linear interpolations of available data should not be used alone, but should be accompanied by a statement of a reasonable range of risk, based on cautious asumptions in the several relevant areas of uncertainty.

PART D

IX. DESCRIPTION OF THIS SET OF REGULATIONS AND ANALYSIS OF THE MAJOR REGULATORY ISSUES

The previous discussions have set forth the necessity of and the scientific rationale for the promulgation today of the OSHA Cancer Policy to identify, classify and regulate potential occupational carcinogens. We do not intend to duplicate those discussions here. The following sections attempt to explain: (1) the procedural mechanisms which will be utilized to accomplish these goals and (2) the additional rationale and policy considerations, that are not discussed in other portions of this preamble, regarding the specific regulatory activity that may ensue.

For ease in discussing the issues, a description of this set of regulations (and issues implicit therein) is presented first. Other issues raised in the rulemaking are discussed in Sections XI and XII below.

A. SCOPE AND PURPOSE (§§ 1990.101 AND 1990.102)

In the proposed regulation, OSHA stated that:

". . . the three proposed model standards would apply to all workplaces in all industries, including the general, construction, maritime and agriculture industries, whenever occupational exposure to the toxic substance, as defined, occurs." (42 FR 54174).

In the course of this rulemaking proceeding, major criticism of this proposed provision was made by certain affected industries. Specifically, representatives of the construction, maritime and agriculture industries argued that the provisions of the model standards and other provisions of the proposed regulation should not apply to their industries. In addition, several participants expressed the view that the proposal, particularly certain provisions of the model standards, should not apply to the regulation of carcinogens as used in research laboratories. Iminent scientists not only expressed such concern (see e.g., Henry Pitot) but also testified as to precautions presently and voluntarily used. In particular, OSHA received correspondence from a number of academic institutions and scientific bodies expressing concern over the potential impact of the cancer policy on the conduct of both instructional and research activities in college and university laboratories, especially in laboratories where carcinogens are presently and necessarily used for the purposes of cancer research. These participants generally urged OSHA either to exclude research laboratories from the application of the proposed Part *per se*, or to exempt them from the regulations issued pursuant to the Part, or to establish a different approach for protecting laboratory workers from that established for other industrial facilities. Many of these participants considered the model standards contained in the proposed set of regulations to be inappropriate, in certain respects, for application to research laboratories. Their arguments for exemption from some provisions of the model standards were based upon the following claims:

(1) Research laboratories use very small quantities of each carcinogen at any one time;

(2) Exposures are brief and infrequent;

(3) The need to use particular substances, including carcinogens, is often difficult to predict in advance;

(4) Research laboratories are, in general, staffed by highly trained personnel;

(5) To impose the same kinds of requirements for worker protection on laboratories as on industrial operations would stifle research, particularly cancer research;

(6) Compliance would be unreasonably expensive.

Although very few of these claims were supported by any specific actual documentation or proof, OSHA is sympathetic to the special circumstances of research laboratories. In a memorandum dated December 21, 1978 to the Director of the Office of Science and Technology Policy, the Director of NCI, Dr. Arthur C. Upton, pointed out:

"The concerns expresed by Professor Roberts and others regarding the application of the proposed OSHA Cancer Policy to research laboratories are indeed important and deserve serious consideration. Having spent many years at the bench, I can fully appreciate the apprehension of scientists who may be concerned not only about the imposition of unneeded control measures, but also about the intrusion of the Federal government into the inner sanctum of the research laboratory. I recall that not too dissimilar concerns were expressed by some researchers when tighter safeguards were imposed on the handling and use of radioisotopes.

"A major concern of researchers appears to center on the necessity to monitor the laboratory environment for contamination by chemical carcinogens. Professor Roberts and others believe that current work practices minimize such environmental contamination and, hence, the potential for laboratory worker exposure. They argue that the cost to monitor would be a needless expense and on that many laboratories could not afford. Despite the belief that the containment of carcinogens is well under control, there are little hard data to support this idea. In fact, there are a number of studies indicating that laboratory workers are often at an increased cancer risk."

* * * * *

"The problem we are faced with is our lack of knowledge regarding the extent and nature of contamination in laboratories engaged in research with chemical carcinogens. The problem is compounded by variations that exist in control technology and work practices among laboratories. The problem could be partially solved and, at the same time, the potential for worker exposure reduced by uniformly requiring that certain minimum safeguards be used by laboratories working with carcinogens. The experience with radioisotopes might well provide a model for implementing universal standards for the handling and disposal of carcinogens. I believe that such basic safeguards should apply irrespective of the carcinogen and without regard as to whether a carcinogen is or is not regulated under the OSHA Cancer Policy.

"As you may know, a subcommittee of the DHEW Committee to Coordinate Toxicology and Related Programs (CCTRP) is developing guidelines for the handling of chemical carcinogens used in the research laboratory. The subcommittee is attempting to define sets of work practices and controls which correspond to different levels of potential exposure. The subcommittee also is preparing safety monographs on the carcinogens now regulated by OSHA and on additional ones designated by the CCTRP. Many of the basic safeguards in the subcommittee's guidelines and those proposed in the OSHA Cancer

Policy are essentially the same as suggested in Professor Roberts' letter of November 8.

"Apart from the minimum safeguards that should be universally applied, there may not be the same need for research laboratories to conform absolutely with an OSHA standard established for industry. Circumstances could be envisioned in which a rigid and comprehensive standard could needlessly inhibit research initiatives. For example, certain research efforts could be obstructed even though the level of potential risk would be lower than that considered in establishing the OSHA standard. In other circumstances, the same standard may be as appropriate for research laboratories as for industry. It seems to me that a standard should have some flexibility to allow for the nature and extent for use of a carcinogen by a research laboratory. Although it would be difficult for OSHA to define every circumstance requiring a special exemption to a standard, it should be recognized that there would be legitimate claims that deserve such consideration."

OSHA believes that exposure of a worker to potential carcinogens is a matter of serious and grave concern and that appropriate protective measures must be implemented, whether the worker is in a laboratory, in a manufacturing facility, or in any other type of workplace. On the basis of the substantial scientific documentation in the Record, OSHA has concluded that as to those scientific issues concerning the identification and classification of potential occupational carcinogens, this Part is uniformly applicable to all workplaces under the jurisdiction of the Act, including laboratories. On the other hand, OSHA is aware that an interagency group has proposed guidelines for the use of many specific substances in research laboratories. The approach of protecting laboratory workers with good processes and good practices may be preferable to specific monitoring of each individual substance employed. OSHA intends to pursue this matter further and reserves judgment for the present on the research laboratories.

Thus, there may be justification for a different type of regulatory response, depending on the type of industry impacted, in implementing this Part. The manner of use and the specific circumstances posed by exposure of workers in research laboratories and in the construction, agriculture, and maritime industries may call for different regulatory approaches, depending on the industry involved and the manner of use of the specific potential occupational carcinogen under consideration. For these reasons, OSHA has concluded that the application of this Part to these industries, as to the regulation of any given substance, should be determined on a case-by-case basis, in the course of the rulemakings taken pursuant to this Part, until a Record can be developed that would support a more appropriate set of model guidelines.

In the case of the construction industry, OSHA notes the existence of an Advisory Committee created pursuant to the Contract Work Hours and Safety Standards Act (40 U.S.C. 333 *et seq.*) and the fact that this Committee has been considering the application of health standards to the construction industry. OSHA intends to refer appropriate questions regarding the applicability to construction of provisions of the model standards to this Committee.

In summary, therefore, OSHA intends that the procedures for the identification and classification of potential carcinogens apply uniformly to such substances in whatever industry or workplace they may be found. The procedures for regulation of potential carcinogens, including the model standards set out in § 1990.151 and § 1990.152, will apply generally to all workplaces, except that certain provisions may be modified or waived for the construction, maritime, or agriculture industries, or for research laboratories, as circumstances may warrant for a specific potential occupational carcinogen regulated under this Part.

B. DEFINITIONS (§ 1990.103)

Definitions in this section are intended to reflect the same scientific conclusions and factual determinations as those found in the proposed regulation, except as discussed below. The language of some of the definitions has been changed in minor ways to express more clearly the intended meaning. Two definitions have been deleted, and two other definitions have been changed in more substantive ways.

(i) Some participants criticised the proposed definition of "suggestive evidence" as being imprecise. After careful review of the scientific issues involved, OSHA has concluded that there are too many variables which affect the degree of confidence in results of scientific studies to provide a single definition of "suggestive evidence" which would cover all eventualities and resolve all concerns raised in this proceeding. Instead, therefore, OSHA intends to rely on scientific judgment and to classify chemicals on the basis of a full scientific review which will consider the limitations of each individual study.

(ii) The proposed definition of "foreign toxic substance" has been deleted because this classification is not used in this Part, as is discussed below.

(iii) The definition of positive results in "short-term tests" has been changed slightly to reflect the extensive scientific evidence discussed in Section VI above. On the basis of the conclusions drawn in Section VI, OSHA has formulated its definition of "positive results in short-term tests" to specify only test systems that OSHA believes, in its judgment, have been "validated" in the sense discussed therein and to not include test systems that have not yet been validated. The definition requires results in two or more test systems for the reasons detailed in Section VI.

(iv) The definitions of "toxic substance" and "potential occupational carcinogen" have been amalgamated into a single definition, because comments contained in the Record reflected some confusion resulting from the original terminology, including the distinction between the two terms.

(v) In the proposed regulation, OSHA did not propose any general definition of the term "substance", and the term is not defined in this final set of regulations, for the following reasons. The definition of "potential occupational carcinogen" is written to cover not only a single substance, but a "combination or mixture of substances." (§ 1990.103) It is OSHA's intention that specific rulemakings to be conducted under this Part may, in appropriate circumstances, be applied to a single substance, to technical mixtures or formulations, to combinations of substances (such as alloys or co-polymers), to categories of substances (such as glass fibers or dyes with a common carcinogenic metabolite), or even to hard-to-define mixtures (such as tars or mine dusts). This approach, in fact, has been OSHA practice in past rulemakings concerned with carcinogenic substances: these have involved relatively pure chemicals (vinyl chloride, 29 CFR 1910.1017), industrial products or processes which may contain only relatively small fractions of the carcinogenic agent (benzene, 29 CFR 1910.1028), categories of substances (various types of asbestos, 29 CFR 1910.1001, or various compounds of arsenic, 29 CFR 1910.1018), and hard-to-define mixtures (coke oven emissions, 29 CFR 1910.1029). OSHA intends to continue this practice and to define the range of substances to be covered in each regulatory proceeding in a way which is appropriate to the scientific evidence and industrial circumstances relevant to the specific case. In other words, OSHA intends no change in how it has resolved this issue in the past in other rulemaking proceedings.

Some participants urged OSHA to define "substance" for the purposes of

this Part in a much more specific and restrictive way. Notable among these arguments were those of Brush Wellman and its witness Dr. Adrianne Rogers (MIT), who wrote as follows:

"From a scientific point of view, it appears that the question of carcinogenicity should be considered separately for each element, compound, mixture, alloy or other material, and that tests of a material of one structure and composition cannot be used as a basis for drawing conclusions of carcinogenicity of materials of different composition or structure because they have one or more components in common. The definition of "toxic substance" should be clarified to include only the specific materials tested and found to be carcinogenic." (Rogers, S. 9).

However, there was voluminous evidence in the Record (including that proffered by Brush Wellman and Dr. Rogers) to show that such an approach would be unjustified and self-defeating. The principal issues involved have been discussed in detail in Sections IV, V, and VII above. The major points that OSHA believes are supported by substantial evidence in the Record include the following:

(i) Most industrial processes yield a complex mixture of chemicals to which workers may be exposed. Even in cases where a technical product has been tested in a bioassay, it is unlikely that any individual workplace will contain exactly "the specific material tested and found to be carcinogenic."

(ii) The exact constitution of a technical product varies between one manufacturing plant and another and even from batch-to-batch within the same plant.

(iii) Where a pure chemical has been tested in a bioassay and found to be carcinogenic, it is scientifically justified to assume that it presents a hazard to workers in any workplace where it is found, whatever other chemicals may be present in technical products or mixtures.

(iv) Many industrial processes produce ill-defined mixtures of chemicals, and in several cases major carcinogenic hazards have been revealed by epidemiologic studies before a specific agent could be identified. One example of an ill-defined mixture already regulated by OSHA is coke oven emissions. Other examples reported in the Record include soot, tars, and oils, chromate processing industries, hematite mining, and woodworking. It would appear to be inconsistent with the purposes of the Act to withhold regulatory action to protect workers from such identified hazards until a specific individual material has been identified as a causative agent.

For these reasons, which are extensively documented in the Record, OSHA intends to define the range of substances to be covered in each specific rulemaking on a case-by-case basis. OSHA expects that each individual case will raise a different combination of issues. These will be fully reviewed scientifically as part of the basis for each proposed rule, and the range of substances to be covered will be defined and subject to comment and resolution in each proceeding. On the basis of substantial evidence in the Record, OSHA believes that it would be unjustified to make a general definition of the range of substances to be covered, either in the excessively restricted form proposed by Brush Wellman in this rulemaking proceeding, or in a less restricted form that would be unlikely to fit the circumstances of specific rulemakings.

C. SCIENTIFIC REVIEW PANEL (§ 1990.104) AND ADVISORY COMMITTEES (§ 1990.105)

Section 1990.104 provides that at any time, the Secretary may request the Directors of NCI, NIEHS and/or NIOSH to convene a scientific review panel* to provide recommendations to the Secretary on the identification, classification or regulation of any potential occupational carcinogen. The Directors will choose the members of the Panel, who should be qualified in the disciplines relevant to the issues raised and be government employees. Where any report is submitted by a Panel, it should be filed in the record of any relevant proceeding undertaken pursuant to the Part, and appropriate public comment will be allowed. OSHA has chosen to utilize the expertise of the federal government research institutes with primary and universally recognized expertise in carcinogenesis and environmental and occupational health. Indeed, OSHA believes that *this* Record in *this* rulemaking reaffirms the breadth and quality of the scientific expertise on carcinogenesis residing in NCI, NIEHS and NIOSH.

Under the Act, and 29 CFR Part 1912, the Secretary may additionally establish an Advisory Committee to provide recommendations on any of a wide range of issues relating to one or more standards, including scientific issues. (Section 7(b) of the Act). The Committees must be composed of a broad cross-section of persons qualified by experience and affiliation so as to present the diverse views of interested groups. In the past, OSHA has convened advisory committees on specific standards for potential occupational carcinogens (e.g., asbestos, the 14 carcinogens, and coke oven emissions). OSHA anticipates that Advisory Committees will in the future also be convened from time to time, thereby giving OSHA additional flexibility in tapping needed scientific expertise outside the Agency.

Advisory Committees will differ substantially in function and constitution from the scientific review panels established under § 1990.104. Thus, the scientific review panels may often have a much narrower scientific focus and be less formal. Since they will be composed entirely of government employees, the scientific review panels would not constitute advisory committees within the meanings of Section 7 of the OSHA Act or the Federal Advisory Committee Act. On the other hand, Advisory Committees would be composed of a cross-section of interests and would be utilized to review issues that go beyond scientific issues. Also, Advisory Committees may only be utilized at prescribed junctures in the rulemaking process, whereas scientific advice from the scientific review panel may be sought at any time for any reason.

The proposed set of regulations did not provide explicitly for a scientific review panel, although OSHA has always believed strongly in the need for the best scientific evaluation of all meaningful scientific data. The concept of providing for evaluation by "outside" scientists is based in large measure upon the suggestions of AIHC, which recommended the creation of an "Evaluation and Classification Panel". However, OSHA is unable to accept AIHC's specific recommendations for the functioning of its proposed panel. For example, AIHC's panel would have been selected by the National Academy of Sciences from lists provided by NCI and non-governmental groups, and would have been solely responsible for the identification and classification of potential occupational carcinogens, subject only to judicial review. Apart from serious questions about the legality and appropriateness of transferring the authority for identifying, classifying, and regulating carcinogens from OSHA to this indirectly-established and non-governmental panel, OSHA believes that AIHC's proposed system would be inefficient in its division of responsibilities, would be subject to unreasonable delays, and would not

*This provision for convening panels on specific substances should be distinguished from § 1990.106(a)(1) which requires the Secretary to request review of the entire Part, at least every three years, by the Directors of NCI, NIEHS and NIOSH, respectively.

ensure the protection of workers. OSHA believes that the system reflected in § 1990.104 and § 1990.105 is much more likely to ensure that OSHA will receive prompt, expert and impartial advice, and to ensure that regulation of potential occupational carcinogens will be expeditious and efficient.

In sum, pursuant to the Act, OSHA has several options available to it to assure that all of the meaningful evidence has been scientifically evaluated. To the extent possible, OSHA has adopted them all. Moreover, the wisdom underlying this system adopted today would appear to have been specifically considered and extensively debated by the Congress on whether there should be an "independent" Board to issue health and safety standards. In the end, the Congress rejected that approach and placed responsibility for issuing standards on the Secretary of Labor, although of course the Secretary could make use of all outside technical and scientific expertise in an advisory capacity.

In this regard, OSHA agrees with the observations of the AFL–CIO in its post-hearing brief, that some of the concerns expressed in the congressional debate apply equally to the AIHC recommended panel. These were: that the Board was not accountable to any one person (Leg. Hist. 1090–1), that many other regulatory agencies had combined standard-setting and enforcement authority and that the key need was for the technical personnel at the operating level of the agency (Leg. Hist. at p. 427–430; AFL–CIO Post Hearing at 26).

D. AMENDMENTS TO THE POLICY AND THE "FREEZING OF SCIENCE" ISSUES (§ 1990.106 and § 1990.145)

As noted elsewhere, OSHA was and is committed to assuring that sound scientific judgment is always utilized in applying this Part to determine whether any particular substance or substances should be regulated as potential occupational carcinogens. Because many participants apparently did not realize this fact, for the reasons detailed below in section IX.I, OSHA has explicitly provided in this Part that amendments should be made to the Part to reflect and respond to expanding scientific knowledge and important scientific developments.

Two mechanisms for amending this Part are explicitly provided. These provisions are intended to ensure that OSHA will consider the "latest scientific data in the field" and that the Policy will reflect the current state of scientific knowledge in carcinogenesis, and incorporate the "best available evidence" pursuant to § 6(b)(5) of the Act. The relevant provisions are as follows. Section 1990.106 deals with scientific review of this Part, at least every three (3) years by the National Cancer Institute, the National Institute for Environmental Health Sciences and the National Institute of Occupational Safety and Health. Section 1990.145 establishes specific procedures to institute an amendment proceeding in conjunction with a rulemaking on a specific substance.

The more general § 1990.106 specifies four circumstances in which OSHA is required to review the Policy: (1) A recommendation for amendment made individually or collectively by the Directors of NCI, NIEHS and NIOSH after a required periodic review; (2) a recommendation for amendment made individually or collectively by each of the Directors of these Institutes, on their own motion; (3) a petition submitted by the public which demonstrates new evidence or issues; and (4) the Secretary's own motion.

More specifically, section 1990.106(a)(1) requires the Secretary to request each of the Directors of NCI, NIEHS and/or NIOSH to review the cancer policy at least every three (3) years, to advise OSHA on whether any significant scientific and/or technical advances since the effective date of this Part warrant any amendment. This periodic review by the Institutes, initiated by the Secretary, is an important mechanism for ensuring that this Part remains consistent with significant discoveries in carcinogenesis and occupational health. Because of their unique positions at the forefront of research, the Institutes may bring to OSHA's attention scientific advances that might not otherwise have been raised.

The second mechanism provided by this Part to ensure that OSHA considers the latest scientific developments is the procedure of § 1990.106(a)(2) that provides for and encourages the Director(s) of the Institutes to recommend to OSHA amendments to this Part based on significant scientific or technical advances, outside the periodic review process. OSHA encourages the Institutes to notify OSHA whenever they become aware of any such evidence. Although OSHA anticipates that periodic review at least every three years will cover most significant advances, it is possible that significant advances in the interim will be made and the amendment of this Part should reflect such advances in a timely fashion by the inclusion of this provision.

The third way specified to require OSHA to review the Part is for a member of the public to file a petition meeting the requirements of § 1990.106(a)(3). The requested amendment must be based on substantial new evidence, and/or substantial new issues. The petition must contain a detailed statement and analysis as to why the petitioner believes that the data, views and arguments presented: (a) are so significant as to warrant amendment of this Part and (b) constitute substantial new evidence or substantial new issues, as further defined. To be considered "new," evidence must be based upon data, views and arguments which differ significantly from those presented in the rulemaking(s) underlying this Part. Thus, OSHA will welcome the submission of substantial new evidence on any issues. OSHA will also welcome the raising of substantial "new" issues, i.e., issues upon which OSHA did not reach a conclusion in this Policy, including the conclusions reached in the preamble, OSHA will not, however, reconsider the same issues based upon the same or merely cumulative evidence.

Lastly, this set of regulations states that the Secretary may, on his own motion, commence a rulemaking proceeding to amend this Part. This essentially expresses the Agency's willingness to initiate an amendment proceeding whenever the Secretary believes that amendment would advance the goals of the Act. The provision does not, therefore, include the requirement that the Secretary initiate an amendment proceeding only when "substantially new" evidence or issues constitute the basis. Similarly the Secretary *may* reconsider this Part, in light of public petitions even where substantial new evidence or issues are not raised. But, the Secretary is not *required* to reconsider or relitigate the Policy in such circumstances. And, the rationale for OSHA's changing its conclusion on provisions of the Policy would have to be aired in an appropriate rulemaking proceeding, accompanied by a reasoned statement supporting the policy change.

Section 1990.106(b) requires the Secretary to respond to recommendations from the Institutes and to petitions by the public within prescribed timeframes. The Secretary believes that the requirement to respond, particularly to public petitions, is an important aspect of keeping the public informed of OSHA's views and actions.

OSHA's possible responses to public petitions whose contents conform to § 1990.106(a)(3) are as follows. The Secretary will either (i) refer the petition to the Directors of NCI, NIEHS and/or NIOSH; (ii) appoint an advisory committee; (iii) deny the petition, giving the reasons therefor; or (iv) commence a rulemaking proceeding to amend this Part. OSHA is not required to respond to petitions that do not meet the procedural requirements of § 1990.106 or § 1990.145. The imposition of a requirement for response in every case where the public makes an insubstantial claim of scientific advance would burden the Agency, deprive it of the capability to respond promptly to those petitions that are based on genuinely new scientific advances, and in essence, would deprive OSHA of the ability to regulate its own priorities. It would also permit the relitigation of the same issues time and again under the amendment procedures.

Where the Secretary determines that the substantial new evidence or substantial new issue is sufficient to initiate a proceeding to amend this Part, the Secretary shall either:

(a) commence a rulemaking proceeding to consider amending this Part; or

(b) commence a rulemaking proceeding to consider amending this Part and consolidate it with the proceeding on the individual substance.

OSHA believes that these provisions eliminate any basis for the criticism of some participants, who alleged that OSHA's proposal would "freeze science" because it would foreclose the future consideration of new scientific advances by the Agency.

Another change from the proposal is an opportunity to amend this cancer policy in the context of standard-setting proceedings on potential occupational carcinogens, based on a demonstration of substantial new evidence and/or substantial new issues, which relate to the substance then the subject of a rulemaking proceeding (§ 1990.145).

These provisions of § 1990.145 were not part of the proposal and their introduction directly responds to comment and testimony in the Record. The definitions of substantial new issues and evidence are the same as those in § 1990.106. The required contents of the petitions for consideration of substantial new issues and evidence are also intended to be identical. In addition, the petition must explain why the proposed amendment relates to the substance at issue.

Petitions must be filed by the deadlines established in the Advance Notice of Proposed Rulemaking, discussed below. In extraordinary cases, petitions may also be filed where the evidence was not available by the deadline, and is submitted at the earliest possible time (§ 1990.145(c)(3)). In the rare case where an Advance Notice of Proposed Rulemaking is not published, conforming petitions must be submitted by the deadline established in the notice of proposed rulemaking.

OSHA believes these provisions will assure the timely consideration of new evidence, will prevent the adoption of standards based on outdated science and technology, and will ensure that significant developments in the field of carcinogenesis will continue to be reflected in OSHA standards-setting activities.

These procedures to intergrate amendment and standard-setting are specifically responsive to the concern expressed in a representative comment by the Dow Chemical Company:

"The record, however, has now made it clear that there is absolutely no assurance that the latest scientific evidence in the field will be permitted to be applied under the proposal to any given regulation of a specific chemical substance. . . . Further, petitions to modify this proposal, if adopted to address the latest scientific data could proceed wholly and separately apart from a contemporaneously initiated rulemaking of a specific substance under the generic regulation. One consequence is an obvious frustration of the proper application of the law. The latest science will not necessarily be allowed in a rulemaking on a specific substance." (Dow Post-Hearing Brief at 7)

A contrary concern was expressed by the Natural Resources Defense Council. NRDC stated that it is unfair for an agency to develop major policy changes of great importance in individual cases, rather than in a "broad rulemaking proceeding," because of limited notice and participation opportunities in the narrower proceeding. NRDC's concern was that a scientific policy issue at stake in a standard-setting proceeding could literally be buried because of inadequate notice. To foreclose that possibility, section 1990.145(d)(iii) requires that the Secretary publish a proposed amendment in the **Federal Register,** whether or not the amendment proceeding is consolidated with the proceeding on an individual substance. In either case, OSHA would, as it has done in the past and in this rulemaking proceeding, affirmatively seek out and encourage participation from all interested segments of the public.

Whenever issues of broad application are addressed in a individual rulemaking proceeding, OSHA will clearly identify these issues in the **Federal Register,** and will notify the public in the same manner as it would if the proceeding encompassed only the broad, general amendment. The provisions of § 1990.145(c)(2) require the petitioner to specify the provisions of the Part believed to be inappropriate and to show that the new evidence is relevant to the specific substance. OSHA will therefore be able to describe the scope and text of any amendment in the notice of the proposed amendment.

In sum, OSHA believes that these newly incorporated amendment procedures will prevent the constant "relitigation" of previously determined issues, yet will allow genuine scientific and policy advances to be incorporated fairly, effectively and expeditiously in this Part.

It should be emphasized that the only way to change this Part is through rulemaking, *i.e.,* a rulemaking proceeding conducted according to one of the above described procedures and subject to the above-described requirements.

OSHA disagrees with AIHC's characterization of the petition to amend as "a time consuming and ponderous mechanism for incorporating into the regulatory standards newly available evidence or data concerning theretofore unresolved issues" (Post Hearing Brief at 190). OSHA does not believe that procedures for amending the cancer policy are unduly burdensome. Further, the potential for combining amend and standard-setting proceedings where a proposed amendment appears limited in scope is expected to expedite the incorporation of policy changes which have limited future application. In the cases where major policy changes are warranted, we believe all interested parties should have an opportunity to participate. This is true whether a major policy issue is considered alone or in conjunction with an individual substance rulemaking proceeding.

E. GENERAL STATEMENT OF REGULATORY POLICY (§ 1990.111)

Section 1990.111 is a general statement of the essential elements of this Part. It does not conflict with and is not intended to supersede any of the more detailed provisions elsewhere in these regulations. With two exceptions, each of the subparagraphs is fully explained elsewhere in this preamble. The two exceptions are subparagraphs 111(j) and 111(k), which are explained below in Section XII.

F. CLASSIFICATION OF CARCINOGENS (§ 1990.112)

In the proposal, OSHA proposed to classify toxic substances into three

substantive categories and to regulate them in different ways.

In general, as more fully discussed below, Category I toxic substances are those whose carcinogenicity, as defined, has been determined in humans or in two or more mammalian species of test animals or in one species if the results of that study have been replicated. Category II toxic substances are those whose carcinogenicity has been reported but the evidence for some reason is only suggestive, as defined, or positive in one species, but not yet replicated. Category III toxic substances are those for which the evidence is inadequate to raise any concern regarding carcinogenicity or where the evidence consists of animal data in a single species that is less than suggestive. (42 FR 54165)

1. Category I and II potential carcinogens

OSHA's rationale for distinguishing between Category I and Category II toxic substances was, firstly, that "false positive" results may arise occasionally, and, secondly, that the degree of scientific confidence in positive results may vary:

OSHA recognizes that "false positive" results may arise occasionally, both through statistical accidents and honest errors in the conduct of single experiments. Accordingly, OSHA recognizes that much greater weight should be attached to positive results that have been replicated in another study than in a single unconfirmed result.

* * * * *

OSHA recognizes that there are other factors involved in carcinogenicity tests which affect the degree of confidence in the results (e.g., choice of strain, spontaneous tumor incidence, duration of experiment, survival, intensiveness and competence of pathological examination, etc.). In addition, OSHA may require detailed review of each experiment, including, where necessary, independent pathological diagnoses, before classifying each toxic substance. (42 FR 54164–54165)

This proposal was commented on by a number of participants in this rulemaking. There was extensive scientific testimony supporting and documenting OSHA's position, cited above, that there are a number of factors involved in carcinogenicity tests which affect the degree of scientific confidence in the results. Other participants argued that some types of data are more convincing than others as evidence of potential carcinogenic risks to exposed workers: for example, all scientific witnesses agreed that convincing positive results in human epidemiological studies would justify classifying a substance in Category I, whereas only a few argued that positive results in short-term tests would be sufficient. For these reasons, there was widespread support for the proposal to classify potential occupational carcinogens into two or more categories. However, a wide range of proposals was made for the criteria for such classification. As discussed earlier, there was a wide range of scientific opinion on the extent of confirmation or replication needed before positive results in human or animal studies can be used to support an inference of carcinogenicity. Some participants argued that OSHA should not regulate workplace exposures at all unless the evidence for carcinogenicity were fully convincing, and some participants claimed that OSHA's proposed definition of "suggestive" evidence was too imprecise.

After review of the extensive comments in the Record, OSHA concludes that its original proposal was basically sound and was well supported scientifically. Accordingly, the proposal is being modified in only minor ways. The rationale for the criteria for Category I and Category II potential carcinogens is discussed in several sections of the preamble. (See, e.g., section V.D.9.)

Where evidence is "suggestive," substances will be classified as Category II Potential Carcinogens. As noted above, OSHA attempted in the proposal to define the term "suggestive," but, based upon the Record in this proceeding, it has not been possible to define the factors which would compel a finding that evidence is "suggestive." "Suggestive" is a commonly used and understood scientific term that requires the exercise of scientific judgment. OSHA believes that the Secretary should, subject to appropriate consideration of priorities, regulate potential carcinogens in cases where scientific evaluation indicates that there is suggestive evidence of carcinogenic hazard. As a legal matter, the Act requires OSHA to take measures to reduce worker exposure wherever there are adequate scientific reasons to infer that such exposure is likely to cause material impairment to health, even if the state of scientific knowledge is such that the existence of the hazard has not been established with complete and absolute certainty. As a scientific matter, both human epidemiologic studies and experimental animal studies are subject to a large number of variables, so that the degree of scientific confidence that can be placed in positive results may vary greatly. This point was documented by voluminous scientific evidence in the record. It was summarized most succinctly by Dr. David Rall (Director, NIEHS), as follows:

I believe that most scientists will be happy to see the introduction of something like Category II, recognizing that some experiments give inconclusive results and allowing us to escape from the dilemma of having to assign all chemicals into "Yes" or "No" categories. On the other hand, scientists always feel unhappy about the application of rigid criteria to complex questions. The scientific decision as to whether a chemical has been shown to be carcinogenic in an animal species requires consideration of all aspects of the experiment, including not only the statistics of the number of tumors but also the pathological diagnoses, exposure regimens, health and nutrition of the animals, and many other factors. Once a chemical is established as a carcinogen in an animal species, there follows a presumption of risk to exposed humans, but the precise degree of risk depends on consideration of other factors, including routes of exposure, metabolic pathways, structure-activity relationships, etc. It is difficult to reduce these manifold considerations to a formula.

On the one hand, there are cases where a single, well-conducted experiment giving clearly positive results should suffice to establish a chemical as a carcinogen and to justify stringent measures to reduce occupational exposure. On the other hand, there are cases where two or even three less conclusive positive results would still leave some doubt. The fact is that scientific experiments never give results that are 100% positive, nor 100% negative. Science deals in probabilities, and carcinogenesis bioassays give results that may fall anywhere on a continuous spectrum of probabilities, extending from 2 or 3% at the lowest to nearly 100% at the highest. Division of this spectrum into discrete categories may be necessary for regulatory purposes, but it is necessarily arbitrary from a scientific point of view. Thus the recommendation of a scientist would be to make the criteria for categorization flexible, and to apply as much scientific judgment to each case as is compatible with legal and regulatory requirements. (Rall, S. 13–14)

Many other witnesses testified about the large number of factors which affect the conclusiveness of positive results and about the crucial role of scientific judgment in judging whether results are conclusive or not.

Because there are so many factors which may limit scientific confidence in positive results, OSHA accepts Dr. Rall's conclusion that rigid criteria cannot and should not be established to separate "conclusive" and "suggestive" results. Instead, OSHA intends to rely on scientific judgment and to classify chemicals on the basis of a full scientific review which considers the limitations of each individual study.

2. Category III Substances

The proposal included provisions for Category III toxic substances (Ex. 1, 42 FR 54172, § 1990.130–133, 42 FR 54186). Category III substances were substances

where there was some evidence of carcinogenicity, but not enough evidence to classify them as Category I or II substances or to take any regulatory action. Under the proposal, if a substance was classified as Category III, the NCI, NIOSH, EPA and FDA would be notified, the decision would be published in the **Federal Register**, and a list of all Category III substances would be periodically published in the **Federal Register**. There were also provisions to reconsider a Category III classification.

There was little comment on the Category III classification. NRDC recommended that the Category III classification be utilized for substances for which the only evidence of carcinogenicity was short term tests. They recommended no regulatory action, but suggested that OSHA establish priorities for further testing.

DuPont (III–134, pp. 52, 67) and AIHC (III–104Q, p. 85) provided for Category III substances in their regulatory proposals. Their definition of Category III would include most substances which would prove to be Category III substances in the OSHA proposal as well as some substances which OSHA's proposal might classify as Category I or II. DuPont and AIHC recommended that the only regulatory response to their Category III substances would be a request to the scientific community for further research and, if deemed necessary, regulation based on other—or non-carcinogenic—effects.

OSHA has carefully considered its proposed position and the few comments which were made. It has decided that it would be advisable not to include a formal Category III classification within this Part. All agreed that it would be inappropriate to take regulatory action based on the evidence which would result in a Category III classification. Requests for further scientific research can be made without going through regulatory procedures. If regulation is needed for non-carcinogenic effects, then the general § 6(b) procedures of the Act are the appropriate approach. OSHA, therefore believes, that having a formal Category III would utilize limited administrative resources which would be better spent on identifying and regulating Category I and II substances.

3. Category IV—Foreign Substances

The proposal also included provisions for Category IV Toxic Substances (Ex. 1, 42 FR 54172; § 1990.141, 42 FR 54187). The proposed regulations provided that when a substance met the definition of a toxic substance but appeared not to be present in any workplace in the United States, the Secretary would publish in the **Federal Register** a notice to classify the substance in Category IV and give the public opportunity to comment on that determination. If the comments indicated that the substance was present or if later information indicated that a Category IV substance was now present, the Secretary would proceed to reclassify the substance as provided for by the Cancer Policy. The proposed regulation also required the periodic publication of the Category IV list in the **Federal Register**.

The reason for the Category IV classification was that sometimes some evidence might be presented to OSHA of the possible carcinogenicity of a substance, although that substance did not appear to be present in any American workplace. OSHA believed it unwise to continue to evaluate the evidence about the substance or propose to regulate it, under such circumstances, because scientific resources appeared to be better spent evaluating and regulating substances which were present in the American workplace and created an immediate hazard.

There were some comments on this aspect of the proposal. AIHC, (Ex. 251A, p. 192), NIOSH (S. III–34, p. 3), and the Environmental Defense Fund (S. IV–30, p. 10) all agreed with OSHA that it was unwise to waste administrative and scientific resources on classifying and regulating substances not present in the American workplace. NIOSH and EDF suggested that they believed that the proposal's procedures would result in too many resources being spent on substances not present in the workplace. NIOSH and AIHC recommended that there be no Category IV to eliminate that problem. EDF recommended that OSHA first determine whether a substance is present before giving any other consideration to it.

All agreed that administrative resources should not be spent on substances not present in the American workplace. Indeed, this was OSHA's belief as well. Thus, upon consideration, OSHA agrees with the commenters that the best way to achieve this goal, is to eliminate the Category IV classification from this final Part. The appropriate time to consider the identification and regulation of potential carcinogens is when a substance is introduced or about to be introduced into an American workplace.

Sections 1990.111(c) and 1990.121(a) of this final set of regulations indicate that this Part shall apply to substances reported to be present in the American workplace. The specific nature of Category I and II definitions will permit an employer to determine which substances that are not present in the American workplace, are likely to be identified as potential occupational carcinogens, if they intend to introduce those substances.

In sum, on review of the Record, OSHA has concluded that the advantages to be gained by maintaining these proposed categories would not justify the expenditures of time and Agency resources necessary to conduct the required scientific reviews. Accordingly, Categories III and IV are not included in this final set of regulations. In cases in which a rulemaking is conducted on a substance proposed for classification into Category I or Category II, and the scientific evidence is found insufficient to justify classification into either Category, OSHA will make a public statement of this finding but will not make a formal Category III designation for such a substance. Similarly, if a rulemaking is initiated on a substance proposed for classification as Category I or Category II, and if information is received which satisfies OSHA that the substance is not found in workplaces in the United States, OSHA will make a public statement of this finding, but will not make a formal Category IV designation for such a substance.

G. CANDIDATE LIST AND PRIORITIES (§§ 1990.121, 1990.122, 1990.131, AND 1990.132)

OSHA believes that this Part establishes a flexible process for screening evidence on substances that may be potential occupational carcinogens and for setting priorities among such substances for full scientific evaluation and regulation as potential occupational carcinogens. The process will take place in three sequential steps, each of which is more fully described below:

(i) the establishment of a 'Candidate List' of substances which, on the basis of brief scientific review, may be considered candidates for further scientific review and possible identification, classification, and regulation as potential occupational carcinogens;

(ii) the establishment of two 'Priority Lists' of substances selected from the Candidate List on the basis of information that suggests relatively high degrees of hazard to exposed worker populations;

(iii) the selection of one or more substances from the Priority Lists for full scientific review with a view to subsequent rulemakings.

OSHA's original proposed regulation did not include either an explicit system

for setting priorities* or a method for screening and classifying the large number of substances reported or alleged to be carcinogenic. However, the proposal drew attention to "the large number of potential carcinogens already identified by NIOSH," and invited the public to submit comments on "the best way to supplement these regulations insofar as those substances identified as 'suspect carcinogens' by NIOSH are concerned" (42 FR 54169, 54170). Furthermore, as pointed out below, in the course of this rulemaking, in response to requests submitted by some participants, OSHA released a preliminary version of the Candidate List prepared by an OSHA contractor, Clement Associates, Inc., scientific regulatory consultants. This list (referred to as the "Clement List" by some participants) was based primarily on a brief scientific evaluation of the data identified in the NIOSH List. OSHA specifically invited *all* participants to submit comments on the Clement List, and specifically to propose ways to set priorities among the substances included in it.

OSHA's adoption of an explicit process for screening candidate substances and for setting priorities is responsive to a large volume of public comment on this point. Many individual witnesses, participants, and Federal regulatory agencies such as FDA and EPA urged OSHA to adopt such a system and to make it public. Furthermore, OSHA agrees with what almost every participant argued, that a rational system of setting regulatory priorities is dictated by the recognition that any Policy as proposed could not and should not transform carcinogen regulation into a mechanical process. Rather, OSHA should, to the extent practicable, regulate the "worst first." However, OSHA believes that under no circumstances should priority-setting slow the important process of reducing human exposures to potential carcinogens.

In addition, the following expectations underlie OSHA's adoption of an explicit process of screening and priority setting:

1. The Department of Labor's internal rulemaking resources will continue to be inadequate to complete standards on all potential occupational carcinogens within a limited period of time.

2. It is not necessarily a prudent use of Agency or Society's resources to regulate immediately every substance that meets the definition of a potential occupational carcinogen. For example, other hazards must be dealt with, as well, the number of exposed workers varies, as does exposure levels and other factors.

3. No workable system can be devised to assess the evidence and then regulate in the foreseeable future all substances on the NIOSH List that meet the criteria for a potential occupational carcinogen.

4. The NIOSH List admittedly includes many substances which are listed as "suspected carcinogens" on the basis of inadequate evidence, and many others which are laboratory "curiosities" unlikely to be found in any workplace, so that a screening process is necessary to limit the range of substances that deserve full scientific review.

Although a large number of comments and suggestions on methods for priority setting were received, both in response to the initial proposal and in response to specific requests for suggestions, OSHA finds after review of the evidence in the Record on this issue that the comments were not particularly helpful for developing a specific priority setting system. The proposals concerning the setting of priorities presented in the Record had three major limitations:

(i) Most priority-setting systems that were proposed were far too elaborate, many of them requiring *full* scientific review of *all* data on *all* candidate substances, together with elaborate risk estimation schemes and in some cases cost-benefit analyses for all substances, before *any* ranking could be undertaken;

(ii) Most proponents of priority-setting apparently assumed that extensive data were available on human exposure and risks, and were unaware of the extremely limited data actually available on most substances;

(iii) Several proposed schemes included numerical systems for estimating risks, involving the assumption that quantitative risk estimation could be conducted reliably and consistently for all substances.

The essence of a good priority-setting system is that it should improve the *efficiency* of a regulatory system by enabling the regulatory agency to treat the "worst first." If the system is too elaborate, it will actually reduce the efficiency of the regulatory system by absorbing the resources of the agency in the priority-setting exercise, to the point where actual regulation is postponed. OSHA regards proposals that its priority-setting system should be based on "systematic review of all the scientific evidence" as disingenuous, both because most of the scientific evidence required for systematic review is lacking, and because consideration of all the scientific evidence available is more appropriately done in the final stage of classification and regulation. To adopt such proposals would achieve little except to delay—if not postpone forever—the initiation of regulation. This approach, which OSHA rejects, has been characterized by some as "Paralysis by Analysis".

Accordingly, OSHA has used the proposals proffered in the Record to suggest a procedure by which OSHA will devise a screening and priority-setting system which will use the limited information available in an efficient way, without attempting to use a formal or rigid system. OSHA believes that its three-step process will accomplish this.

The publication of a Candidate List of Potential Occupational Carcinogens is provided by § 1990.121. This list will include substances which are present in American workplaces and which, based upon OSHA's brief review of available data, appear to be candidates for further scientific review or for regulation as potential occupational carcinogens. The list may also tentatively designate substances as candidates for classification as Category I or Category II potential occupational carcinogens, although some substances will be listed merely as candidates, without mention of any category. Annual publication of the list in the **Federal Register** is required. The Secretary will consider and respond to petitions concerning the inclusion or exclusion of any substance from the Candidate List (§ 1990.122).

The regulation generally defines "available data" to mean: (1) data submitted by any person; (2) data referred to in NIOSH's list of suspect carcinogens; (3) data found in the U.S. Public Health Service, Publication No. 149; (4) Monographs of the Toxic Substances Control Act International Agency for Research on Cancer (IARC); (5) The Inventory of Chemical Substances prepared by the Administrator of EPA; (6) the Annual Report of the Secretary of HHS to the President and Congress; and (7) other relevant data of which the Secretary has actual knowledge (§ 1990.121(a)). For administrative and other practical reasons, the Candidate List will not

*The omission of an explicit priority system from the proposal did not mean that OSHA was oblivious to the importance of priority setting. Indeed, OSHA discussed possible schemes for addressing the backlog of substances identified by NIOSH and invited comment on the best way to implement the policy (42 FR 54169, 54170). OSHA intended that priority setting would continue to be a traditional exercise of Agency discretion, subject to the guidance of section 6(g) of the Act, which states:

"In determining the priority for establishing standards under this section, the Secretary shall give due regard to the urgency of the need for mandatory safety and health standards for particular industries * * * work places or work environments. The Secretary shall also give due regard to the recommendations of the Secretary of Health, Education and Welfare regarding the need for mandatory standards in determining the priority for establishing such standards."

specify the data that were reviewed. OSHA will identify the relevant data to any interested party upon written request.

The regulation permits the tentative designation of a substance by Category, but does not require it. OSHA tentatively will designate a substance if after the brief scientific review, the quantity and nature of reported evidence permit such a preliminary designation.

The compilation of the Candidate List will assist OSHA and other interested parties in several ways. In the first place, it is expected to reduce the number of substances subject to review from the several thousand "suspected carcinogens" in the NIOSH List to no more than a few hundred which survive an initial scientific review. In addition, OSHA believes, and the Record supports, that the establishment of the Candidate List will improve OSHA's ability to set priorities and to select substances for regulation under this Part; will provide the public useful information by informing them that a substance is a candidate for closer scientific review and possible regulation; will stimulate early public comment to assist OSHA to evaluate the available scientific data before it; will assist the research community to focus its resources; and will help OSHA become cognizant of relevant data before it sets priorities for regulation.

OSHA emphasizes that the Candidate List is not a final scientific determination that any listed substance is a potential occupational carcinogen, nor is it intended as even a pre-classification warning. The failure to include a substance or its subsequent deletion from the Candidate List is not intended to detract from the value of any data concerning that substance, in the context of any OSHA enforcement or rulemaking proceeding. No legal rights or burdens are intended to be conveyed or imposed by the inclusion or exclusion of a substance. However, the Secretary will welcome information that may be relevant to the inclusion or exclusion of any substance on the List, and will respond to any petitions thereon (§ 1990.122).

For the purpose of compiling the Candidate List, OSHA intends that a "brief scientific review" will initially consist only of review of data contained in items (2) to (6) of the list in § 1990.121(a). The inclusion of a substance in item (5), the EPA Inventory of Chemical Substances; compiled pursuant to the Toxic Substances Control Act, will be used as *prima facie* evidence for the presence of the substance in workplaces in the United States. Reports of carcinogenicity presented or cited in items (2), (3), and (4) will be subjected to scientific review, to the extent required for the purposes of compiling the Candidate List. At this stage of scientific review, underlying data will not be sought or reviewed except as provided, non-positive results will not be considered in relation to positive results, and special factors such as those listed in § 1990.144 will not be considered. If a substance appears to be a candidate for inclusion in Category II, data on short-term tests will be assembled from readily available sources (such as the Environmental Mutagen Information Center and computerized bibliographies) and scientifically reviewed. Substances included in item (6), the Secretary of HHS's annual Report to the President, will generally be included in OSHA's Candidate List without further review. Additional information falling under items (1) or (7) will be incorporated as it comes to the attention of the Secretary.

OSHA is at present preparing the first Candidate List and will make it public within three months after the effective date of this Part. A preliminary version of the Candidate List was prepared and released to participants in July 1978, with an invitation for comment. That draft List differs from the forthcoming Candidate List in three major respects which were dictated by resource constraints: only substances listed in the NIOSH List of "suspected carcinogens" were considered, results of short-term tests were not reviewed, and the EPA "Inventory of Chemical Substances" was not available.* Instead, the draft List was based on two other sources of information on the occurrence of substances in U.S. workplaces: the EPA "TSCA Candidates List" and the U.S. International Trade Commission's 1976 data base. The number of substances tentatively identified as candidates for Category I or II was 488 based on the former source and 187 based on the latter source. OSHA anticipates that the number of substances included in its first Candidate List will lie between these figures.

OSHA believes that a brief scientific evaluation process of the kind specified above is sufficient and appropriate to accomplish the purposes of compiling and making public a Candidate List. It is OSHA's judgment that requiring a more intensive review process, at the early, non-regulatory stage of screening evidence, would compromise OSHA's ability to perform its main regulatory functions by absorbing all agency scientific resources. Primarily for this reason OSHA rejects the recommendation of Dr. Lester Lave (Carnegie-Mellon Univ.) that OSHA publish a list of potential carcinogens based on the "most complete knowledge of the toxicity of substances in each plant" (Lave S. 37).

The inclusion in the Candidate List of substances listed in sources other than the NIOSH List was recommended by several parties, and OSHA agrees that review of additional sources is appropriate. OSHA has also incorporated the suggestion of AIHC, that EPA's "Inventory of Chemical Substances" be used as part of any preliminary classification process. (Exhibit 251 D at 4–5).

Many participants expressed mixed feelings as to whether the Candidate List should be made public. On the one side, all agreed that OSHA should have a system for priority-setting. On the other hand, whether the Candidate List should actually be made public generated significant public comment, some from the same participants. AIHC expressed concern about the value of tentative classifications on such a list "since the data are unevaluated." Other parties raised the issue of "stigma," based on their perceptions of inclusion of substances based on "unevaluated data." For example, the Society of the Plastics Industry, Inc. stated in a post-hearing comment:

> "First of all, unevaluated lists of substances being considered as potential candidates for regulation as carcinogens should not be treated lightly. While the parties to OSHA's proposed cancer policy proceeding were anxious to see the preliminary categorization, the publication of a list which had not been at all scrutinized is regarded by industry as inappropriate. . . . For example, the erroneous listing of a substance as being under consideration of regulation as a carcinogen can cause the two extremes of public reaction—one, concern about the use of the material and, the other, erosion of the credibility of governmental and other scientists in assessing carcinogenic hazards. In addition the scientific resources of government, industry, and the public are diverted to investigating and rebutting erroneous classifications. Furthermore, the incorrect association of materials, which have been shown to be innocuous and safe for their intended uses, with well known, potent carcinogens can have a detrimental effect on their manufacture, marketing and use. For such reasons, OSHA should take much greater care in this area" (Exhibit 263 at 16–17).

However, as pointed out above, OSHA believes that AIHC and the Society of the Plastics Industry were

*Several participants who commented on this draft List erroneously concluded that data on substances included in it had not been subjected to critical review. To the contrary, at least two studies on each substance had been subjected to full scientific review.

incorrectly assuming that data in the Clement List and the Candidate List were or are to be "unevaluated." OSHA emphasizes that the primary purpose of the list is to indicate which substances should be subjected to fuller scientific review. Designating the list "Candidate List" should be sufficient to communicate this intent.

In fact, OSHA believes that making the list public, with the invitation to submit information concerning the evaluation of baseline data, and the required annual updating, will convey the tentative nature of any listing and underscores OSHA's willingness to review the Candidate List.

The second step in setting priorities for regulation under this policy is the establishment of two more refined Priority Lists. Section 1990.131 requires the Secretary to establish two priority lists, one for approximately 10 Category I candidates, the other for approximately 10 Category II candidates. The listing of a substance is, again, not OSHA's scientific determination that the listed substance is in fact, a Category I potential carcinogen or a Category II potential carcinogen. (Section 1990.131.) Inclusion on a Priority List means that the Secretary has or intends to thoroughly review all of the relevant and meaningful scientific and technological evidence concerning the listed substances ahead of other substances on the Candidate List. The order within the priority lists is not intended to convey the order of additional scientific evaluation of data and the Secretary can alter listings accordingly. The Secretary reserves the right to regulate a substance as a potential occupational carcinogen, regardless of whether such substance appeared on any of the published Candidate or Priority Lists. The Priority Lists are not intended to create any legal rights.

Section 1990.132 contains some of the factors OSHA will consider in setting priorities for regulation. These are: (1) the estimated number of exposed workers; (2) the estimated levels of workers' exposure; (3) the reported levels of exposure causing increased incidence of neoplasms in humans and/or animals; (4) the extent to which regulatory activity can reduce cancer risk and other occupational and environmental hazards; (5) the extent to which the substance has a molecular structure similar to the molecular structure of another substance that meets the definition of a potential occupational carcinogen; (6) whether substitutes exist that would pose lower risks, or whether there is other evidence that the social and economic costs of regulation would be small; and (7) the relationship of the substance to regulatory activities of other agencies.

Section 1990.133 provides that the Priority Lists be published in the **Federal Register** every six months, and that notices requesting relevant information and comment may accompany the lists.

The above provisions directly respond to comments in this rulemaking Record, which reflected a consensus by virtually all interests represented, that the final cancer policy should include specific provisions for priority-setting.

OSHA has previously described the development of regulatory priorities in the health hazard area as considering the following factors: the number of exposed workers; the severity of the hazard; the existence of information relevant to hazard identification and control; recommendations from NIOSH; petitions for standards; and court decisions and other factors affecting enforceability. Of these factors, severity is considered the most important [see Exh. 77 to Appendix 42, Secretary of Labor's Brief, *National Congress of Hispanic American Citizens* v. *Marshall* (No. 79–1222 U.S.C.A. D.C.)]

OSHA's priority factors also are consistent with those established by other regulatory agencies and by the Regulatory Council. Dr. Donald Kennedy (Commissioner, FDA) described the factors considered by his agency in the setting of priorities as the relative carcinogenic potency of the substance, the number of persons exposed and the dosage or level of exposure. (Kennedy, Tr. 493–497). EPA utilizes a similar system, basing its priorities on an analysis of relative potencies and the number of persons exposed (Tr. 2359, Jellinek, S. 2). Dr. Bates (NIEHS; FDA) testified that he agreed with the approach to priorities which stated as its goal, "Let's get the worst things out of the way first," and that this would be "highly desirable" from the point of view of regulatory agencies.

The factors listed in § 1990.132(b) are not intended to cover all the relevant information which might ideally be considered to estimate the magnitude of a cancer hazard presented by a substance, and the consequent priority for regulatory intervention. As noted in the language of the Part, the setting of priorities involves consideration of many factors, including subjective judgment. More important, critical numerical information is in most cases lacking on such major factors as the number of workers exposed, the extent of their exposure, and the risks accrued per unit of exposure. For this reason, the setting of priorities for subsequent rulemaking activity necessarily must involve a large element of scientific judgment applied to usually incomplete data.

The first factor, the number of exposed workers, is fundamental to assessing the extent of both the health problem and the need for regulatory intervention. The second factor, the levels of their exposure, refines the degree of risk for the individual, and for the affected population. As Dr. Bates (NIEHS; FDA) testified, "The individual's risk of developing cancer is higher as you increase the exposure level, and the principle holds that the lower the exposure . . . the fewer people who are going to get cancer." (Bates, Tr. 611–612). The third factor, the levels of exposure that are reported to cause an increased incidence of neoplasms, is a very rough measure of the likelihood of risk per unit of exposure. Although, for reasons detailed above and below, OSHA has concluded that numerical estimates of cancer risk are too uncertain to serve as the basis for setting permissible exposure limits. OSHA believes that consideration of the possible magnitude of risk may be relevant and can be useful for priority-setting. It is prudent to assume that a substance which induces neoplasms in animals at relatively low levels is likely to pose a greater hazard to workers (other circumstances being equal) than a substance which induces neoplasms in animals at only higher levels.

The fourth factor, *i.e.*, the effectiveness of regulation in reducing both the cancer risk and other health and safety risks, is a recognition of the interplay between this Part and other hazards to workers, particularly as to the overall need for regulation. OSHA intends, when it considers regulating any substance, to ascertain whether other physical and chemical properties constitute occupational hazards, to the extent that they are known, from exposure to that substance and to include protection against those hazards in the standard when doing so would not delay a regulatory response to reducing cancer risk from that substance.

The fifth factor, the molecular similarity between a potential carcinogen and other regulated potential carcinogens, is less clearly related to the likely magnitude of the risks posed by a substance, and may in fact be given less weight by OSHA than other listed factors. However, other things being equal, it may be justifiable to give slightly higher weight to a substance that belongs to a class of substances known to pose hazards to workers.

The sixth factor, whether substitutes exist that would lower risks, or whether there is other evidence that the social and economic costs of regulation would be small, is another one of the priority-setting factors. OSHA is concerned about the relative costs of regulations in terms of health risks, and about the cost-effectiveness of regulations in the sense discussed by witnesses such as Dr. Lave (Carnegie-Mellon Univ.) and Dr. Zeckhauser (Harvard Univ.). If two possible regulatory activities would protect equal numbers of workers and all other circumstances are similar, there is an argument for proceeding first with the regulation with the smallest social and economic costs. OSHA is aware of problems of equity raised by this principle, however, and will use this factor cautiously in setting priorities.

The final specific factor listed for consideration in priority-setting is the co-ordination of regulations on a given substance with other regulatory agencies. There is an obvious advantage in such co-ordination if it can be achieved. Although it is difficult to use this factor formally in drawing up the Priority Lists, it may be appropriate at times to initiate rulemaking for a substance which is relatively low in the Priority Lists in order to achieve inter-agency co-ordination.

Under the priority system in these regulations, some Category II potential carcinogens, in appropriate circumstances, may be regulated before some Category I potential carcinogens. Since categorization reflects some degree of confidence that the substance causes cancer, while the priorities approach considers several other relevant factors, no inconsistency would be involved in such a decision. For example, where a substance meets the criteria for Category II potential carcinogen, because evidence of concordance may be absent, yet where large numbers of employees are exposed to high levels, OSHA may determine that the substance should be regulated before a Category I potential carcinogen to which only a small number of workers may be exposed. At the hearing, the CPSC Chairman testified that CPSC may give a higher priority to a substance where evidence of carcinogenicity is "weaker" than the evidence concerning another substance, if there is a potential for significantly greater exposure in terms of the number of persons exposed, and other relevant considerations. (Byington, Tr. 2090).

This Part emphasizes the judgmental component of priority setting. Section 1990.132 states that, "The setting of priorities is a complex matter which requires subjective and policy judgments. It is not appropriate to establish a rigid formula or to assign predetermined weight for each factor. The identification of some of the elements is to guide the OSHA staff and the public in the development of priorities. It is not intended to create any legal rights with respect to the setting of priorities."

Retaining flexibility in setting priorities is consistent with the recommendations of many participants. In this regard, AIHC testified, "Priorities for regulation would depend upon the exercise of judgment based on all available information, particularly information as to actual workplace hazards, rather than any predetermined or automatic order. Regulations most needed would be developed first." (AIHC, Tr. 3607)

In sum, OSHA believes a requirement for a priority setting system will improve the quality of rulemaking proceedings (in terms of the length, sequence and focus), should assist the Agency in determining rational priorities, and ultimately should lead to more efficient regulation of workplace exposure to potential carcinogens by providing more health protection to the American worker. The actual system itself, however, is in the Agency's discretion and may change as circumstances warrant.

H. PROCEDURES FOR RULEMAKING (§§ 1990.141, 1990.142, AND 1990.147)

The steps OSHA will take after issuing the priority lists are as follows. OSHA will select one or more substances which it intends to regulate, will begin relevant technological and economic studies, and in such cases will issue Advance Notices of Proposed Rulemaking, which will describe these studies. In almost every such case, OSHA then expects to initiate rulemaking, by issuing either a notice of proposed rulemaking, pursuant to section 6(b) of the Act, or an emergency temporary standard, pursuant to section 6(c) of the Act. The model standards attached hereto (§§ 1990.151 and 1990.152) will serve as guidelines for OSHA in developing the proposal and the public in anticipating OSHA's regulatory stance. A more extended discussion of the role of the model standards is found elsewhere.

In more detail, the regulatory provisions governing this activity are as follows. Section 1990.141 applies after the initiation of an economic and/or technological study to analyze the ability of impacted industries to comply with the different levels of employee protection under consideration. The form and content of the studies will also vary with the circumstances. Although OSHA expects that most substances selected for study will have appeared on the priority lists, the Agency has retained the discretion to initiate regulatory activity for substances not so appearing, as well.

Within 30 days after the study is initiated, the Secretary will normally issue an Advance Notice of Proposed Rulemaking (ANPR), which will provide information to the public on the scope of the feasibility study, the available data on health effects, and an estimation of when the Secretary anticipates the issuance of a proposal (§ 1990.141). It will also indicate the deadline for the public to file feasibility information, and the procedural requirements including the timeframes that must be met before substantial new evidence or substantial new issues in support of an amendment to this Part (as provided by § 1990.145) will be considered.

The ANPR was not explicitly provided for in the proposal, although ANPR's have been utilized in the past as one common means of gathering information by all Federal agencies and are encouraged by Executive Order 12044 on improving government regulations. Under the proposal, OSHA contemplated utilizing ANPR's in a similar fashion. However, in viewing its past experience, OSHA noted that while OSHA was conducting its feasibility studies, which can take 6 to 9 months, and analyzing the health and other data, response by the public to gather information has often not been synchronized with OSHA's effort. Thus, many interested persons either were not aware of OSHA's inquiry or would wait until the publication of the proposal in the **Federal Register** to put forth their best efforts. As a result, OSHA and the public had different needs after the proposal was issued: OSHA had completed most of its independent work and was ready for detailed public input in a rulemaking proceeding; on the other hand, many members of the public were often just "gearing up" and would request more time to prepare their presentations adequately. Under this Part, the ANPR will allow—and indeed require—the public and OSHA to synchronize their information-gathering efforts at the same time. OSHA recognizes that the information provided in an ANPR may not be as detailed as that found in the proposed regulation. In fact, some of the data, including feasibility data, are likely to be preliminary. Nonetheless, the issuance of ANPRs will enable OSHA and all interested persons to gather and analyze

technological, economic and other relevant information. The model standards will serve as guides to the likely content of the proposal. Interested persons should be able to complete the bulk of their technological and economic studies before the actual proposal is issued and would only then have to reevaluate that data in light of the proposal.

In contrast, most or all of the data on health effects are likely to be available to the public when any ANPR is issued. Therefore, in most instances it will be appropriate to expect the interested public to review the available data long before the issuance of the proposal so that substantial new issues or substantial new evidence can be raised in timely fashion. Early submission of new issues and new evidence is necessary to ensure that they can be considered adequately without delaying the rulemaking process. As discussed elsewhere, the Secretary will establish a deadline for the filing of new evidence or new issues. The deadline will usually be 60 to 90 days from the publication of the ANPR, but will vary, depending on factors such as the anticipated date of the actual proposal and the volume and complexity of the scientific information. Interested persons may request the Secretary to extend the deadline if circumstances so require. It should be noted that while these ANPRs will generally be issued, there will be some situations, such as where an emergency temporary standard is necessary, in which the advance notice may be omitted.

Section 1990.142 is based on the statutory options for initiating rulemaking; i.e., standard setting under § 6(b) which will include protective provisions based on the guidance of the relevant model standards and will list the issues expected to be at issue; or the issuance of an emergency temporary standard under § 6(c) along with a proposal for a permanent standard. These provisions are changed from the proposals in three major respects.

A significant change from the proposal in this rulemaking relates to time requirements. The proposal contained requirements for OSHA to issue proposals on all potential occupational carcinogens within prescribed time limitations, but there were no time requirements concerning procedures to be taken after the issuance of proposals. In contrast, this Part establishes time requirements after the issuance of proposals. For example, time requirements are established for the close of the comment period, the commencement of any hearing and the promulgation of final standards. The intent is to promulgate final standards within one year from the issuance of proposals, unless there are specific reasons for granting extensions.

In reviewing OSHA's history in promulgating final standards, it is clear that the time period from the issuance of proposals to the issuance of final standards has been longer than what might be considered a reasonable amount of time. For example, the final inorganic arsenic standard was issued 40 months after the proposal. Contrast this with the time from proposal to final standard where the Act establishes timeframes: vinyl chloride, only 6 months; and acrylonitrile, only 7 months. By establishing these timeframes in this regulation, OSHA is making a public commitment to the issuance of final standards (or a statement as to why no final standard will issue) which is an extremely important matter and not to be taken lightly. Implementation of final standards protects employees; proposals are merely a step in that process, and workers remain at risk in the interim. When the government and the public expend valuable resources on rulemaking proceedings, it is reasonable to expect that the proceeding will be brought to a conclusion within a reasonable amount of time, one way or another.

The purpose of these timeframes is not to provide a legal basis to prevent or in any way delay promulgation of final standards. Rather, they are intended to provide specific targets for completion of the standard-setting process, so that any failure to comply or unreasonable delay will be made public.

A requirement to issue proposals within certain time periods was included in the proposed regulation, but is not included in this Part, for several reasons. First, unlike the proposal, priorities will not be determined by an identifiable event such as receipt of information from the public. Instead, priorities will be based upon policy judgments taking into account numerous factors. Moreover, in deference to OSHA's limited resources, OSHA recognizes that it will not be able to regulate every potential occupational carcinogen in the immediate future. In these circumstances, it would not serve a useful purpose to require the automatic issuance of proposals within a prescribed timeframe.

The second important change from the proposal is the way in which the model standards will be used in individual rulemakings. Each rulemaking proposal will follow the format of the model standards and will include the major industrial hygiene provisions represented in the paragraph headings, unless the Secretary explains why he believes such a provision is inappropriate. In contrast to the proposal, this Part makes explicit that the Secretary has discretion in each rulemaking proposal, to include, delete or change any protective provision under each paragraph heading. These more detailed regulatory provisions are intended to guide OSHA in drafting the proposals and are expected to vary among proposed substances. OSHA notes an extended discussion of the role of the model standards in this Part is contained *infra*.

The third significant change in the initiation of regulatory activity is the use of emergency temporary standards to initiate regulatory activity for Category I potential occupational carcinogens. The use of an ETS was to be mandatory for Category I toxic substances under the proposed regulation, but is now discretionary in this final regulation (see the discussion in section K below).

I. GENERAL PROVISIONS FOR USE OF ANIMAL AND HUMAN DATA (§§ 1990.143 AND 1990.144)

The principal purpose of this generic rulemaking is to facilitate the regulation of toxic substances posing potential carcinogenic hazards to workers. By reviewing most of the general scientific issues concerning carcinogenesis and by establishing general rules concerning the use of scientific information on carcinogenesis, this proceeding is intended to improve both the efficiency and specificity of individual rulemakings, ensure uniformity of treatment and avoid continual relitigation of issues already clearly resolved. However, carcinogenesis is a complex process which is still not adequately understood scientifically. Hence, it is necessary to strike a balance between some limitation of scientific discussion, which is necessary to avoid regulatory paralysis, and the flexibility to consider exceptional cases and to accommodate new scientific advances.

In the proposed regulation, OSHA attempted to strike this balance between regulatory efficiency and scientific flexibility by reviewing each of the major issues in carcinogenesis and drawing conclusions on each. Further discussion of these major generic issues in the individual rulemakings was to be foreclosed "in general". However, flexibility was to be achieved in two major ways. First, a system was proposed whereby regulatory presumptions could be rebutted, either for specific named reasons or "for any other scientific reason". Second, OSHA

stated its willingness to consider amendment of the generic regulations whenever new scientific advances so warranted.

OSHA's proposal was criticized from several perspectives. Some participants criticized the proposals for rebuttal, particularly the general criterion for rebuttal, as excessively flexible and tantamount to re-opening all the supposedly foreclosed issues. Others criticized the proposal as not providing sufficient opportunity for the consideration and possible incorporation of new scientific developments. This Part is responsive to both criticisms by increasing the opportunities for the introduction of new evidence and consideration of new issues where appropriate, while more clearly reaching conclusions on the many issues which were fully presented and analyzed in this proceeding.

In the first place, the most cogent objections to the proposal presented by scientific witnesses were related to the procedures made for accommodating new scientific knowledge. A number of witnesses described rapid advances in scientific knowledge of some aspects of carcinogenesis, (especially the study of mechanisms, structure-activity relationships, short-term tests, and quantitative estimation of risks) and recommended that provision should be made for incorporating new knowledge as it is acquired. Accordingly, this final regulation includes more specific procedures for the amendments of the policy to reflect new scientific knowledge. Section 1990.106 provides for general review of the policy at regular intervals or at the request of either the Directors of NCI, NIEHS, or NIOSH, or members of the public. In addition, § 1990.145 provides for the consideration of new issues or substantial new evidence whenever such new issues or new evidence arise in the course of rulemaking on a specific substance. These two provisions will provide ample opportunity for both this Part and rulemakings subject to it to be kept in step with scientific advances.

In the second place, OSHA's proposal prompted the detailed presentation of scientific evidence in the Record. This evidence not only provided primary scientific documentation of the major issues in carcinogenesis discussed in OSHA's proposal, but also brought the Record up to date by permitting OSHA to incorporate the scientific evidence generated in 1977 and 1978. As shown in detail in the analysis presented in Sections IV–VIII, this scientific evidence presented at the hearing generally provided ample and overwhelming support for OSHA's original proposed conclusions. Only one substantial new scientific issue was raised in the hearing—the possible use of metabolic and pharamacokinetic information. Although this information was shown to be of considerable scientific interest (and possibly be useful in the future), no appropriate proposal for its use in identifying and classifying potential occupational carcinogens was made. OSHA therefore concludes, after exhaustive review of the evidence, that its proposed conclusions on the major scientific issues were, in general, correct.

A third aspect of the scientific evidence presented at the hearing, however, were examples of unusual or exceptional cases which several witnesses claimed would constitute exceptions to OSHA's general conclusions. These cases are fully reviewed in OSHA's analysis of the Record in Sections III–VIII above. Although OSHA concludes that most of these supposed exceptional cases are purely hypothetical or speculations about future advances, OSHA is persuaded that provision should be made for considering such cases, if they should in fact arise in individual rulemakings pursuant to this Part. Accordingly, this final regulation includes two specific provisions for considering such cases. First, § 1990.145 provides a mechanism for the consideration of substantial new issues or substantial new evidence whenever such issues or evidence arise in connection with a rulemaking on an individual substance. Second, exceptions to the general criteria may also be considered, thus, OSHA's substantive conclusions on issues and evidence raised in the generic rulemaking are reflected in the provisions of § 1990.143 and § 1990.144. Section 1990.143 sets out 11 specific provisions concerning the use of human and animal data in identifying and classifying potential occupational carcinogens. Section 1990.144 establishes provisions for considering exceptional cases, specifying minimum criteria which must be met by evidence on purported exceptions before it will be considered. The purpose of establishing these minimum criteria is to permit the full consideration of all scientific evidence that is sufficiently strong to justify consideration of exceptions to the general provisions of § 1990.143, while excluding evidence that is irrelevant, repetitious, or clearly insufficient to warrant review. As explained in detail above, these criteria have been established on the basis of substantial scientific evidence presented in the Record. They have been chosen in such a way as to permit consideration of evidence that may warrant exceptional treatment, while excluding consideration of evidence that has already been shown in this Record to be speculative or insufficient.

OSHA concludes that the provisions of §§ 1990.143, .144, and .145 will suffice to provide the scientific flexibility needed to accommodate new scientific evidence and unusual or exceptional cases. At the same time they will greatly improve the speed, efficiency, and consistency of rulemaking procedures by providing an explicit and uniform framework for using scientific data, by limiting continual re-introduction and re-litigation of arguments already fully resolved scientifically, and by excluding evidence and arguments that are repetitious, frivolous or irrelevant.

J. LIMITATIONS ON ISSUES TO BE CONSIDERED IN THE RULEMAKINGS (§ 1990.146)

As stated above, one of the important objectives of this Part is to increase the efficiency of the rulemaking process by avoiding continual re-discussion and re-litigation of issues, already resolved. Section 1990.146 contributes to this objective by prescribing the issues that the Secretary may consider in each rulemaking on a specific substance or group of substances. It operates in conjunction with §§ 1990.143, 1990.144, and 1990.145, which specify general provisions for the use of human and animal data and provide for limited exceptions. Section 1990.146 limits the evidence that may be considered in each rulemaking proceeding to evidence directly relevant to the issues raised by the regulation of the specific substance subject to the rulemaking, unless § 1990.145 permits an exception.

Section 1990.146 specifies the following issues that may be considered:

(a) Whether the substance, group of substances or combination of substances subject to the proposed rulemaking is appropriately considered in a single proceeding.

As discussed earlier, there are many cases where it is appropriate for OSHA to establish standards for groups or categories of substances considered together, or even for hard-to-define mixtures. For the reasons stated, the definition of the range of substances and/or mixtures to be included in the individual standard-setting proceeding may involve a number of complex questions which ultimately must be resolved by good scientific and engineering judgment. OSHA believes it

is, therefore, entirely appropriate that these questions should be open for comment and resolution in the specific rulemaking on the substance or group of substances.

(b) Whether the substance or group of substances subject to the rulemaking meets the definition of a potential occupational carcinogen set forth in § 1990.103, including whether the scientific studies are reliable.

This corresponds to issue (a) of § 1990.113 and 123 of the proposed regulation. The purpose of including this issue is to provide for an opportunity to subject the scientific studies to scientific review and ultimately to the exercise of scientific judgment as to whether the studies bring the substance within the definition of a potential occupational carcinogen. The scientific issues upon which OSHA has reached a conclusion, including conclusions in the preamble to this Part, may not be raised under the rubric of scientific judgment or reliability or any other provision of this Part.

(c) Whether the available data can appropriately be applied to the range of substances covered by the rulemaking.

There are several circumstances in which the data which provide the evidence for carcinogenicity of a substance may not be automatically applicable to the range of substances or mixtures of substances covered by the rulemaking. For example, a compound may have been tested, whereas workers are exposed to a technical mixture, or *vice versa*. Epidemiological data may refer to one technical mixture, whereas workers may nowadays be exposed to another. If a class or category of substances is to be regulated, epidemiologic or experimental data will usually be available for only a few members of the class. In all these cases, the use of data obtained with one substance or mixture to justify the inference of risk to workers exposed to another substance or mixture is the subject of legitimate scientific debate, and should be open for full comment and resolution in the individual rulemakings.

(d) Whether the information, data and views that are submitted in accordance with § 1990.144 are sufficient to warrant an exception to this Part.

The issues that may now be raised under this provision would have been foreclosed in the proposed regulation. As noted in the explanation of § 1990.144, the Secretary believes it is more appropriate to establish evidentiary criteria for these issues rather than foreclosing them entirely. Since evidence may be received in accordance with § 1990.144, the Secretary must consider whether the evidence is sufficient to warrant an exception to the Policy.

(e) Whether the data, views and arguments that are submitted in accordance with § 1990.145 are sufficient to warrant amendment of this Part.

Since substantial new evidence and substantial new issues may be raised in accordance with § 1990.145, the Secretary must consider whether such data, views and arguments are sufficient to warrant an amendment to this Part. It should be emphasized that "substantial new issues" are important issues that are new or issues that OSHA did not present conclusions on in the Cancer Policy, including the underlying rationale as described in the preamble. Moreover, the submission of "substantial new evidence" in accordance with § 1990.145 is sufficient to require the Secretary to consider either "new" or "old" issues argued and raised by such evidence. In this way, OSHA will be able to consider "the best available evidence," while avoiding relitigating issues that are resolved by this Part.

(f) Whether the potential occupational carcinogen meets the criteria for a Category I potential carcinogen or a Category II potential carcinogen.

The need to consider this issue is self-evident. It should be noted that this issue does not permit the relitigation of the criteria for Category I and Category II potential carcinogens. Rather, in considering the issue, the Secretary is required to apply the criteria set forth in the Policy, except as noted below.

(g) The environmental impact arising from regulation of the substance.

As the draft and final Environmental Impact Statement to this Part point out, environmental consequences of the regulation of individual substances, if any, are usually dependent on the specific characteristic of that substance. Therefore, it is appropriate to investigate in the course of the substance specific rulemakings, the environmental impacts of each regulation. That is also the time that actions can be taken to ameliorate any possibly unfavorable environmental impacts which may be revealed.

OSHA will follow the requirements of the National Environmental Policy Act, the Council on Environmental Quality's regulations and the Department of Labor's implementing regulations during the course of an individual rulemaking.

(h) Any issues required by statute or Executive Order.

This issue recognizes that future court decisions interpreting the Act and amendments to the Act may require OSHA to consider additional issues. It also is a recognition that OSHA will consider additional issues that are required by Executive Order and are not inconsistent with the Act (or this policy). It should be noted that no legal rights are created by this provision. Rather, the legal right would have to be based upon any independent legal obligations recognized in court decisions, or created by an amendment to the Act, or otherwise required by the Act.

(i) The determination of the lowest feasible level to control exposures to Category I Potential Carcinogens primarily through the use of engineering and work practice controls, including technological and economic considerations.

This definition is basically the same as the provision in proposed regulation (§ 1990.113(c)).

As stated in § 1990.111(h), "Worker exposure to Category I Potential Carcinogens will be reduced to the lowest feasible level, primarily through the use of engineering and work practice controls." OSHA intends that this issue is foreclosed. However, the determination of the lowest feasible level including technological and economic considerations must, of course, be an issue in the individual proceeding. Although OSHA believed that it was clear that the determination implicitly included technological and economic considerations, because of the concerns expressed in the Record, the Part explicitly expresses these considerations.

(j) The determination of the appropriate employee exposure level, consistent with the Act's requirements, for Category II Potential Carcinogens.

This issue includes the elements of § 1990.123(c) of the proposal, which provided for worker exposure levels to be based upon other toxic effects where there is no standard or where the present standard is inadequate. This Part allows the Secretary greater discretion, as to whether a permissible exposure limit should be established for any specific Category II potential carcinogen under consideration in an individual rulemaking, and, if so, upon what health considerations the permissible exposure should be based. Thus § 1990.111(i) provides: "Worker exposure to Category II Potential Carcinogens will be reduced as appropriate and consistent with the statutory requirements on a case-by-case basis in the rulemaking proceedings on individual substances. Any permissible exposure limit so

established shall be met primarily through the use of engineering and work practice controls." Since the level for Category II carcinogens will be determined on a "case-by-case basis", the setting of levels must be an issue for the proceeding.

(k) Whether suitable substitutes are available for one or more uses of Category I potential carcinogens.

The proposal provided for setting a "no occupational exposure level" when suitable substitutes existed for Category I potential carcinogens to encourage substitution. The provision has been included in the final Cancer Policy with changes. See the extensive discussion of the suitable substitutes provision in Section XII.b of this preamble and the statement of regulatory policy in § 1990.111(k). Section 1990.146(k) indicates that all issues relevant to substitution may be considered in a rulemaking on a permanent standard for a Category I substance.

(l) Whether the provisions of the proposal and of § 1990.151 and § 1990.152 (model standards) are appropriate, except as limited by § 1990.142.

The proposal (§ 1990.113(d) and .123(d)) would have permitted changes in the model standards based upon unique properties or uses of the substance or inappropriateness or infeasibility of the standard. The language has been changed to more adequately reflect OSHA's intentions. The role of the model standards is discussed in detail elsewhere. These model standards are expected to be the focal point in determining the final regulatory requirements for each substance-specific standard. To the extent that the proposed standard differed from the model standard, the appropriateness of the proposal would, of course, be at issue. It should also be noted that the sufficiency of protection afforded by the proposal and the model standard would also be an issue in the proceeding. Thus, if a party believes that the proposal and the model standards do not provide sufficient employee protection, that issue can be raised. Likewise, if a party believes that the proposal and model standards "over-regulate" in any specific case, this too is an issue to be decided in the individual rulemaking. However, as noted above, the primacy of engineering and work practice controls may not be challenged under this provision in the individual rulemakings.

One issue that was expressly permitted in the proposal is whether the Secretary correctly determined that the classification should not be rebutted. See § 1990.113(b) and 1990.123(b). Although this Part does not expressly provide for this issue, any issue that could have been raised under the proposed provision may be raised under this Part. Since the format (presumption—rebuttal) has been changed, the issues that may be raised appear in different places in this Part. For example, under the proposal, the allegation that the evidence on a substance is only "suggestive" may be used to rebut a Category I classification, thus leading to a Category II classification. Under the Cancer Policy, the issue of whether the evidence is "suggestive" may be raised in determining whether a potential occupational carcinogen should be regulated as a Category I or II potential carcinogen. See also, e.g., the proposed § 1990.111(a)(2) and § 1990.144(b) and § 1990.146(c) of this Part.

K. PROVISIONS OF STANDARDS FOR POTENTIAL OCCUPATIONAL CARCINOGENS (§ 1990.142(a)(2), (a)(3), AND (b))

The Part provides for three types of standards that may be applied to potential occupational carcinogens. When proposing a standard for a substance classified as a Category I potential occupational carcinogen, the Secretary will issue a notice of proposed rulemaking which follows the provisions of § 1990.142(a)(2). He may also issue an Emergency Temporary Standard which follows the provisions of § 1990.142(b). At the time of proposing a standard for a substance classified as a Catetory II potential occupational carcinogen, the Secretary will issue a notice of proposed rulemaking which will follow the provisions of § 1990.142(a)(3). Final standards are to be issued according to the provisions of § 1990.147, which specifies timeframes for issuances of final standards and that any substantial differences between proposed and final standards should be explained.

For Category I potential occupational carcinogens, the principal provisions of the proposed standards are the following:

(i) a permissible exposure limit, which "shall be set as low as feasible to be achieved primarily through engineering and/or work practice controls";

(ii) other specified provisions included in the model standard, which is to serve as a guideline.

These provisions are discussed and justified below under *Methods of Compliance.*

OSHA had proposed that exposure to all Category I substances required an ETS, because "(a) employees are exposed to grave danger . . . and (b) that such emergency standard is necessary to protect employees from such danger."

This final set of regulations provides that the Secretary may initiate rulemaking for a Category I potential occupational carcinogen by issuing an Emergency Temporary Standard (ETS) pursuant to § 6(c) of the Act and § 1990.111(1) of this Part (§ 1990.141(b)). The change from the proposal is the deletion of the requirement to issue an ETS when rulemaking is begun on all Category I substances. (See proposed § 1990.112).

OSHA has concluded that the proposal's policy determination, i.e., that continued exposure to a Category I substance constitutes a "grave danger" within the meaning of section 6(c)(1)(A) of the Act, is correct. The proposal's statement of reasons explained:

The proposition that cancer, and substances that cause cancer, pose a grave danger to man does not need lengthy discussion. As pointed out, the nature of a cancer hazard differs from other types of toxicity. Employees exposed to carcinogens risk incurable, irreversible and in most cases, fatal consequences. These consequences may be irreversibly set in time. No symptomatic evidence of the development of the cancer may be apparent to the employee during a long latency period. A single exposure episode may be sufficient to cause cancer. These factors . . . establish the grave danger.

Evidence and testimony introduced into the Record of this proceeding have provided abundant support for this policy determination. As discussed above, the essentially irreversible and incurable nature of many occupationally related cancers has been described by witnesses. In addition, it is widely accepted that exposure to carcinogens for very short periods can begin the carcinogenic process and epidemiological evidence is consistent with this view. OSHA notes that its determination that substances which may cause cancer pose a "grave danger" to employees has judicial endorsement. See *(Dry Color Manufacturer's Assn. Inc.* v. *Dept. of Labor,* 486 F. 2d 98 (CA 3, 1973); *Vistron Corp.* v. *OSHA,* (No. 78–3020 CA 6, 1978).)

However, OSHA has determined that the question of whether a particular emergency standard is necessary to protect employees from such grave danger, the second prong of the statute's test, is more appropriately left for determination in each case. OSHA believes it should retain the flexibility not to issue Emergency Temporary Standards where, for instance, the limits of short-term exposure reduction already have been reached voluntarily. In such a case, although OSHA's application of the priority factors listed

in § 1990.132(b) and otherwise, might signal regulatory activity leading to a permanent standard, there may be no compelling need for an emergency standard. In other cases, the level of the agency's resources including compliance, legal and technical personnel, at a given time, may suggest that employee health may be more effectively protected by concentrating those resources in work on permanent standards.

This is not to say that the Agency disavows the judgment that in most such cases, employee exposures should be reduced as soon as possible. Scientific support for reducing employee exposure and instituting other protective measures upon identification of Category I potential occupational carcinogens was provided by Drs. Saffiotti and Griesemer (Tr. 1001–1002). In addition, Dr. Selikoff testified: "With good scientific judgment, I would urge that exposure to carcinogens cease as soon as they are identified" (Tr. 1995). Dr. Fishbein "back(ed) fully" the issuance of an ETS once a substance is placed in Category I (Tr. 1651) as a confirmed carcinogen.

Like the model permanent standards, the model Emergency Temporary Standard is more flexible than the proposal's so that the provisions needed to be implemented immediately will vary with the substance, the industry, the previous regulatory history, and other relevant factors. Most general provisions of the proposed model have been retained; they cover the essential elements such as notification of use, housekeeping, monitoring and exposure control housekeeping information and training, and medical surveillance. As discussed in more detail under the model standards, these types of general provisions will be required for ETS's unless good reason exists not to do so. The model ETS provisions will be used as a guideline for the detailed requirements. Thus, for example, some form of monitoring will usually be required, but the frequency, accuracy and other detailed requirements will be determined on a case-by-case basis.

For Category II potential occupational carcinogens, the principal provisions of the proposed standard are the following:

(i) reduction in worker exposure "as appropriate and consistent with the statutory requirements on a case-by-case basis in the rulemaking proceedings on individual substances. Any permissible exposure level so established shall be met primarily through engineering and work practice controls."

(ii) other specified provisions included in the model standard, which is to serve as a guideline.

Of these provisions, the requirements of the model standard and the direction to rely primarily on engineering and work practice controls are discussed fully in Section X below on *Methods of Compliance*. The first provision, however, for reduction in worker exposure to be set on a case-by-case basis, is not discussed in Section X and represents a change from the provision in the proposed regulation. The proposal was that permissible exposure levels for Category II toxic substances should be set on the basis of toxic effects other than carcinogenesis, unless a standard already existed. This proposal was criticized on a number of grounds. First, it was argued that the regulatory consequences of Category II as outlined by OSHA provide no incentive to industry or to other Federal agencies and in no way guarantee that the necessary scientific studies to determine whether a substance should be classified in another category will be carried out in a reasonable amount of time (EDF, Tr. 7329).

Similarly, the Natural Resources Defense Council urged that the question of the carcinogenicity of Category II substances be resolved within a specific period of time. (270, pp. 24–26. See also Tr. 6357–58—Dr. Wolfe). "Category II classification should result in immediate action of some kind and emergency animal bioassay tests and human epidemiology programs should be initiated to determine if the substance should be elevated to Cat. I . . . the standard should specify a testing protocol once classified as Cat. II."

OSHA believes these concerns are valid. Since additional tests might well establish that a Category I classification is appropriate, new research efforts are necessary so that the Agency can reassess the carcinogenic potential of a Category II substance. OSHA intends to utilize all possibilities provided under the Toxic Substances Control Act to develop data, and to officially inform EPA when a Category II classification is made, before OSHA completes its regulatory activity. Official notice of Category II classifications and requests for development of additional data will be sent to NCI, NIEHS, NIOSH, EPA, FDA, and CPSC, at the same time (See Wrenn, Tr. 105). In addition, Category II standards may prescribe such monitoring and medical surveillance as the Secretary concludes may be necessary or appropriate for the development of information regarding a substance's carcinogenicity.

Some participants questioned the appropriateness of classifying a substance under Category II on the basis of its carcinogenic potential, yet setting an exposure level on the basis of the acute or chronic effects other than cacinogenicity. The Environmental Defense Fund and the National Association of Manufacturers expressed the concern that regulating substances for non-carcinogenic effects under the "cancer policy" would slow down OSHA's response to regulating occupational carcinogens (Tr. 7329). NRDC's representative questioned the rationale of the regulatory scheme, testifying that:

"Under Category II, the present proposal does not make any sense to me at all. OSHA proposes to set exposure levels based on toxicity data that has nothing to do with cancer, even though the reason that a substance is in Category II is because there is some evidence that it causes cancer." (Tr. 6299)

NRDC suggested that the answer to this problem is to require as much worker protection against the carcinogenic risk as possible using existing control technology (270, pp. 24–26).

OSHA has decided not to include a requirement in the cancer policy that all Category II substances be regulated on the basis of potential carcinogenic effects at the lowest feasible level, or some variant thereof, as suggested by NRDC. The evidence may not justify that action in some situations. But OSHA agrees that its proposal precluded consideration of potential carcinogenic effects in setting the PEL in all circumstances. While individual substances are classified under Category II on the basis of specified scientific criteria, there may be a range in the quality or quantity of the evidence indicating carcinogenicity meeting these criteria. In some cases, for example where the evidence of carcinogenicity concerning a Category II substance is strong (even though insufficient to bring it into Category I), and other factors such as the number of exposed workers and the potential impact of limiting exposure seem to warrant regulatory action, it may be appropriate to set the exposure level on the basis of carcinogenic effects in order to meet the Agency's statutory responsibilities.

OSHA disagrees with NRDC that it is necessarily inconsistent to classify a substance under Category II because there is some evidence it causes cancer, yet to set the level on the basis of other toxic effects. The setting of a permissible exposure limit is only one aspect of regulation. As discussed above, classification under Category II is primarily intended to trigger further research and data gathering, so that the Agency can ascertain if the substance should be elevated to Category I.

Furthermore, the fact that a toxic substance is a suspect carcinogen may accord it a higher priority than a toxic substance that is not a suspect carcinogen (all other factors being equal). See discussion at Section XVII and IX–B1. Thus, there are reasons plainly relevant to the Cancer Policy for classifying a substance under Category II even if a PEL for Category II were based solely on other toxic effects of that substance. Moreover, in certain circumstances, rational use of the Agency's resources may well suggest that so long as a substance is being regulated under Category II, the substance's other toxic effects should be regulated as well.

On the other hand, OSHA agrees that there may be circumstances where it would be inappropriate for the Agency to base a Category II exposure level on other toxic effects. Where the data on toxicity are limited, further research may be necessary before regulation on the basis of toxic effects would be appropriate. Where the data are disputed, lengthy rulemaking proceedings are likely. In either case, the swift and generally limited regulatory response contemplated for Category II Potential Carcinogens would be impeded. Consequently, the Agency believes that toxic effects cannot always be the governing criterion for setting a Category II PEL, although toxic effects will certainly be relevant in many cases.

These comments, and others in the Record, have persuaded OSHA that there are no criteria that are equally appropriate for establishing an exposure level that would be valid for all Category II potential occupational carcinogens. A major problem is that most Category II substances are in this category precisely because there is insufficient information on their toxicity. Accordingly, the principal value of the categorization is to draw attention to the lack of information and to set in motion new studies. To this extent, the Category II standard is likely to be, to some extent, a standard that will hopefully stimulate data gathering. During the period of data gathering, which may be anticipated to be relatively short, the permissible exposure level should be set at a value which reflects the information available on the substance at the time of rulemaking. OSHA's wording of the standard in this final regulation reflects this conclusion.

L. FINAL ACTION (§ 1990.147)

The final action provision is basically self-explanatory. It provides a system whereby the Secretary must timely conclude rulemakings commenced, pursuant to this Part and comply with certain other requirements.

X. THE MODEL STANDARDS

A. THE ROLE OF THE MODEL STANDARDS

OSHA is issuing two model standards as part of its final cancer policy regulations. They are an Emergency Temporary Standard and a Permanent Standard Model. These model standards are changed from the proposal, both in concept and substance.

The role of the model standards in the cancer policy was extensively discussed in this rulemaking. In particular, API submitted lengthy and helpful post hearing comments on the model standards.

Based on a review of the record and the policy considerations of the Agency, OSHA has made the following decisions. The paragraph headings in the model standards which represent the major industrial hygiene programs envisioned by Section 6(b) of the Act, must be included by the Secretary in every rulemaking proposal initiated under this "cancer policy unless he explains why he believes such a program is inappropriate. In contrast, the policy gives the Secretary complete discretion to include, delete or change any specific provision under each heading.

As in the proposal, three basic policy determinations, (i) that the employee exposure limits for Category I shall be "the lowest feasible" (ii) that the permissible exposure level shall be achieved primarily through engineering and work practice controls, are incorporated in the models and; (iii) that required Medical examinations and personal protective clothing and equipment must be provided at no cost to the employee.

The reasons for assigning these various roles to these components of the models are as follows. First, the decision to routinely incorporate the paragraph headings of the model standards (with the exceptions stated above) in each proposal stems from OSHA's findings that these headings represent generally applicable elements of industrial hygiene programs to protect the health of employees. Thus, the paragraph headings in the models will appear in each proposed standard, unless OSHA explains why the program would be inappropriate. For example, in the model standard for both Category I and Category II substances, the various paragraph headings include medical surveillance and training and information and others. Each of these broadly stated industrial hygiene program elements was endorsed by the entire spectrum of the professional industrial hygiene community in the record. OSHA believes that all these programs are important constitutents of an effective employee protection program. The detail and rigor of such programs, however are suitable for determination only in specific rulemakings, in the context of exposure to specific substances, their properties and uses, affected industries and work operations.

The difference in Category I and Category II model standards is as follows. As in the case of the detailed provisions under each paragraph heading, the Secretary does not "presume" that the inclusion of the four headings of "permissible exposure limits", "hygiene facilities", and "signs and labels" in a proposed standard is necessary. The inclusion or deletion of such a program from a final standard will be determined based solely on the record of the rulemaking proceeding.

To further clarify the role of these provisions, OSHA has made two other changes from the proposal. First, OSHA has deleted from the models most of the quantitative detail, such as frequencies of monitoring and other specifications such as method for floor cleaning. Second, the appropriateness of these newly "generalized" industrial hygiene provisions, can easily be placed in issue in an individual substance rulemaking by a party without alleging the "uniqueness" of a property or use (contrast proposed § 1990.113). The section of these final regulations which sets forth this changed role in the models is § 1990.142.

In addition, the final regulation specifically identifies as an issue in subsequent § 6(b) proceedings whether the provisions of the proposals are appropriate and sufficient (§ 1990.146). This issue was changed from the proposal's version of whether there were "unique properties or uses that make the specific protective measures of the proposed standard inappropriate or infeasible" (proposed § 1990.113, 123) OSHA has made this change in response to comments that requiring a showing of "uniqueness" was either unreasonable or did not truly conform to OSHA's stated intention to allow "appropriateness" to be discussed in most proceedings.

OSHA also agrees with the AFL–CIO that the subsequent rulemaking proceedings should consider "whether any additional measures not contained in the proposed standard should be included to improve its effectiveness"

OSHA had intended that the question of adequacy of protection be an issue in the § 6(b) rulemakings. In the final regulation, therefore, to clarify the point, the word "sufficient" has been inserted after "appropriate" to assure that additional protective provisions may be urged in the § 6(b) rulemakings.

OSHA anticipates that these changes in language will allow flexibility in adapting the model standards to specific substances, while retaining the advantages of issuing models as guidance to OSHA and the public in future proceedings.

These revisions in the format and substance of the model standards do not change the two basic policy determinations that were incorporated in the proposals and continue to be incorporated in the final model standard for Category I substances. One policy determination was explained in the preamble to the proposal as follows:

> OSHA intends to permit no deviation from the general policy, that the employee exposure limits and permanent Category I standard shall always be the "lowest feasible level". OSHA does not believe that it should deviate, in the substance by substance rulemakings themselves, from the position proposed to be established in the rulemaking, namely, that when dealing with human carcinogens it is appropriate to set a level which assures the lowest feasible risk to workers. If and when substantial evidence is available to show that "safe" or "no-effect" levels can be predicted for exposure of human beings to carcinogens, OSHA will act to amend this basic policy decision reflected in this set of regulations proposed today.

OSHA's reasons for this policy were also articulated in the preamble to the proposal as follows:

> The policy decision to reduce exposures to as low as feasible, is not made without sound support. As has been discussed above, a no-effect or threshold level may theoretically exist for any specific carcinogen. As yet, however, there is no satisfactory scientific basis for determining such levels for any given population. Thus, as has been proposed, any human exposure to a carcinogen, even at levels below those which induced positive effects in man or in test animals, would be considered by OSHA to present a potential cancer risk as a policy matter. We do not know whether "safe" of "no-effect" levels exist for carcinogen and, if so, what they may be. Therefore, attempts to set finite exposure limits are not directed at determining "safe" levels of exposure but rather are attempts to determine the lowest feasible levels.

The proposal recited extensive scientific evidence supporting this position (42 FR 54165). We believe the scientific evidence adduced in this policy provided even more extensive support. (See Section V.D.10).

The other major policy determination reflected in the model standards, i.e. OSHA's statement, on methods of compliance is fundamentally unaltered from the proposal and, similarily, is not intended to be changed in rulemaking conducted pursuant to the procedures established by this cancer policy. It is, in brief, the requirement that permissible exposure limits be achieved primarily through engineering and work practice controls, except in the case of an ETS where respiratory protection may also be relied on. An extensive discussion of this policy is found below.

OSHA also does not agree with some participants that the purpose of all protective provisions merely is to control emissions or dispersions of contaminated material to a numerical permissible exposure level. Rather, as the Act itself recognizes, employee health is promoted by some programs whose purpose is somethng other than directly reducing employee exposure. Thus medical surveillance and the knowledge of adverse health effects gives employees information they need to make decisions about their jobs and their futures. Similarly, Congress directed that employees be advised by labels or warning of all hazards, (§ 6(b)(7)), and that employees or their representatives have the right to observe monitoring or measuring. The reason for these requirements is that they contribute to employee health by promoting an informed workplace and encouraging employees to act as "private compliance officers," not that in the narrow sense they are simply components of an exposure control strategy.

A different issue was raised by AISI (#219, T. at 30) and others who recommended that the final cancer policy should contain no model standards because of legal flaws and policy objections. To the extent that this suggestion was premised on the lack of flexibility inherent in the models, OSHA believes the changed role of the model standards goes far to meet these concerns. In sum, the inclusion of model standards is expected to improve OSHA's ability to respond appropriately to scientific evidence concerning potential occupational carcinogens and thereby help transform the Cancer Policy into tangible employee protection.

B. DESCRIPTION OF THE PROVISIONS OF THE MODEL STANDARDS

The following is a discussion of the general requirements and specific provisions contained in the model standards.

There are three provisions of the model standards that will apply in all circumstances and may not be changed except by amendment of this Part under §§ 1990.106 or 1990.145. They are: (1) worker exposure to Category I Potential Carcinogens will be reduced to the lowest feasible level; (2) permissible exposure levels will be achieved primarily through engineering and work practice controls; and (3) medical examinations and personal protective equipment required by individual standards will be provided at no cost to the employee.

All proposals regulating potential occupational carcinogens will contain provisions for certain general requirements, such as monitoring and medical surveillance, unless the Secretary explains why such general requirements are inappropriate. The specific provisions under each general heading will be decided on a case-by-case basis. The details contained in the model standards will serve as guidelines. The following discussion provides OSHA's rationale for including the various provisions in the standards. The discussion of the detailed provisions is provided for background information and more guidance.

(1) Scope and Application (Paragraph a)

All standards will have a Scope and Application provision, to indicate who is covered by the standard and who is not covered.

The actual coverage of each standard will be decided on a case-by-case basis.

One issue in the Cancer Policy proceeding was the intended coverage of each individual standard. Exemptions were urged for industries such as the construction industry (see e.g. Tr. 7128–29); certain maritime segments, agriculture and laboratories (see API comments at 23, comment No. 67; See discussion on laboratories in Section IX–A). Some argued that it would be impractical and unreasonable to apply the model standards in these industries because of special circumstances such as high turnover, limited and intermittent exposure and transient job sites.

The Agency has concluded after review of the evidence on this record, and based on its own experience administering other health standards, that these issues are particularly suited for resolution in the individual substance proceedings. For example, where construction workplaces dominate exposure situations, it may be appropriate to devise special regulatory requirements for construction. Thus, exclusions from regulation for specific industries may be urged in the rulemaking proceedings.

The Agency believes based on the Record, that the scientific conclusions and policies are equally applicable to all employees in every industry. Identifying and classifying substances pursuant to scientific principles enunciated in this Cancer Policy will be done without reference to industry designation. No evidence was introduced to show that all employees in any particular industry were free from exposure to potential carcinogenic substances.

The question of whether, in considering the regulation of a specific substance, different industries and uses should be regulated differently is still open. Since reasons for excluding industry segments from specific standards or portion of standards usually would involve a finding that it would not be feasible to include them, such decisions would be based on the facts concerning a particular substance and are not amenable to resolution on a generic basis.

In addition to possible exclusion for certain industries, provisions for action levels and percentage exclusions will be considered on a case-by-case basis. Although other OSHA standards have utilized both "action levels" and "percentage exclusions" to limit the scope of the standard or certain substantive requirements, OSHA did not include these concepts in the proposed model standards because they were not thought to be generally appropriate for all cases for carcinogen regulation. However, the Agency did not intend to foreclose the application of these concepts in future rulemakings.

The rulemaking proceeding has not altered OSHA's views concerning the lack of universal applicability of these regulatory devices. However, a significant segment of the public endorsed their use in previous standards, and has urged that OSHA include in this Cancer Policy a statement of intention to appropriately utilize action levels and percentage exclusions. OSHA believes that this suggestion has merit, and has included, in the final model, standards, references to these devices, to be used "when appropriate."

Because of the amount of public interest in these issues, a review of the relevant record follows. The action level concept was supported by many participants in the rulemaking proceeding. Industry witnesses supported the use of the concept to minimize employer burden. These included representatives of the NAM (T-7673); SPI (T-6655, 6708, 6703, 6661, 6702), and Northern Petrochemical Company (T-8095).

At what level to establish the action level was widely debated. Although it was generally acknowledged that no one level would be appropriate for all substances, some participants preferred establishing a policy of setting an action level at a set ratio to the permissible exposure level, with the possibility of setting a different level in exceptional cases. (See, e.g., SPI at 6675.)

According to NIOSH an action level of ½ the permissible exposure was selected for the Standards Completion Project, based on statistical considerations, *i.e.*, that at that level, there was only a "small probability" that the actual exposure level is above the PEL. Although one half the PEL has been chosen in some standards covering carcinogens, (e.g., vinyl chloride), the "small probability" cited above may or may not be considered sufficiently "small" when dealing with Category I substances. In appropriate circumstances, even that "small" probability of overexposure may be considered too high. It should be noted that the Standards Completion Project, with its uniform ½ action level, was not intended to cover substances with carcinogenic potential. OSHA may also use an action level to trigger various regulatory requirements in a standard for a Category II substance for which no PEL is established.

The AFL–CIO, along with API and Dr. Robert Harris, testifying for OSHA, have recommended that action level determinations be based on the observed (measured) variability in exposure situations (Post-hearing brief, at 99, see also, Harris, Statement, API, Exh. 219–6).

Additionally, the use of an action level can serve other purposes. For example the recently promulgated lead standard (43 FR 54992 *et seq.*) set the "action level" to implement new protective provisions, such as medical removal protection. Thus, that standard provides that in specified cases of adverse medical findings, employees be removed from work having an exposure to lead at or above the action level. The "action level" was chosen in part as a level low enough to "enable the gradual excretion of the excess lead."

OSHA, therefore, has left the determination of whether to set an "action level," the choice of specific requirements to be triggered by an "action level" and the setting of an action level, to be made in the context of the record developed in each rulemaking conducted pursuant to this part.

Many participants also endorsed provisions for exclusion of certain mixtures, or "percentage exclusions" in the models. (See, e.g., B.F. Goodrich M7–2; Adhesive and Sealant Council #91–9; AIHC pp. 51–52; PMA #116–12, 3M #239–9; etc.). Most comments on this subject cited the OSHA use of such exemptions in its standards for 14 carcinogens (29 CFR 1910.1003–1016), with the percentage exclusion set at 1.0 percent for certain substances and 0.1 percent for others. The comments were concerned in large part that mixtures containing trace amounts of regulated substances would mandate expensive control devices. For example, it was argued that "many areo space propellants and aviation lubricants contain trace amounts of carcinogens which cannot be eliminated. Failure to provide exemptions would have enormous adverse impacts . . ." (To same effect see, e.g., #141–2; 144–2; #259–23.)

OSHA agrees that percentage exclusions may be appropriate in some cases. In other cases, it may not be possible to establish an appropriate percentage exclusion. Therefore, the Agency prefers to leave this issue for the substance-specific rulemakings where relevant information can be considered. Accordingly the percentage exclusion issue can be appropriately raised in any rulemaking under this Part.

(2) Definitions (Paragraph b)

As with Scope and Application, it is clear that a definition section must be provided to define the important terms utilized in standards on individual substances.

(3) Permissible Exposure Limits (Paragraph c)

Under the Cancer Policy, the permissible exposure level for Category I Potential Carcinogens will be reduced to the lowest level feasible. This requirement can only be changed by amendment of the Cancer Policy.

The proposed model ETS and permanent standard for a Category I carcinogen provided that employee exposure would be reduced to the lowest level feasible. What exposure level is in fact "feasible" for an individual substance would be determined in the rulemaking proceeding on that substance. The Secretary explained that the basis for this decision was that, since there is no satisfactory basis for determining a "safe" or threshold level for exposure to carcinogens, any human exposure to a carcinogen presents a potential cancer risk. Therefore, in keeping with the requirement in section 6(b)(5) of the Act to "assure" that no employee will suffer material impairment to health, to the extent feasible, attempts to set exposure limits would be directed at determining

the lowest feasible levels. Section XI contains an extensive discussion of the technological and economic considerations relevent to determining the lowest feasible level for worker exposure to potential carcinogens.

The permissible exposure limit for Category II Potential Carcinogens raises different issues. As noted in the discussion of Category II Potential Carcinogens section of the preamble (see section IX–K), any PEL may be determined as appropriate, consistent with the record. Because of the nature of the evidence of Category II Potential Carcinogens and the role other toxic effects may play in establishing any PEL's, this is an issue that is not foreclosed.

Whether ceiling limits are appropriate will be established on a case by case basis. In past regulations on carcinogens, OSHA has sometimes provided for a ceiling (see, e.g., vinyl chloride and benzene) and other times has not done so (see, e.g., coke oven emissions). This determination has been based upon the unique circumstances of each record. The record in this proceeding does not permit a uniform decision on whether there should be a ceiling limit; therefore the issue of whether to establish a ceiling limit will be decided on a case by case basis.

Whether eye and dermal limits are appropriate will also be established on a case by case basis. Issues such as the likelihood that the regulated substance is absorbed and systemically distributed are the bases for deciding whether to establish eye and dermal limits. Therefore this issue is best left to resolution upon the record in each rulemaking proceeding.

(4) Notification of Use and Emergencies (Paragraph d)

There will be a notification of use provision, unless the Secretary explains why such a provision is inappropriate.

Employer notification of use to OSHA is an important provision of regulatory standards; there are millions of workplaces in the United States and it is impossible for OSHA to know all or even most of the workplaces that use carcinogenic substances. Therefore, it is often essential for OSHA's enforcement of new standards to have reports of the use of potential carcinogens. Reporting of emergencies, defined in the proposal as releases over the ceiling limit, also aids OSHA's enforcement of standards, provides valuable feasibility information and aids in monitoring the effectiveness of OSHA standards. Because, a "ceiling limit" may not always be included and some participants suggested that massive or uncontrollable releases should constitute emergencies, the definition of an emergency will vary from case to case.

Criteria for the application of the notification of use requirement will be determined on a case by case basis. Although most participants felt notification of use would provide OSHA with valuable information, several participants felt that a broad notification of use provision would be too burdensome in many instances.

OSHA's intent is to avoid imposing reporting requirements that are unduly burdensome; indeed, in the past, OSHA has imposed limited notification of use requirements (see, e.g., benzene). Issues such as whether other Agencies may require similar imformation and if there are other reasonable means for obtaining this information will also be considered.

(5) Exposure Monitoring and Measuring (Paragraph e)

(a) There will be a provision for exposure monitoring and measurement unless the Secretary explains why such a provision is inappropriate.

Monitoring is one of the touchstones of OSHA health standards; without some form of monitoring, employers would not know the extent to which employees are exposed to carcinogenic substances and whether controls were needed. Employees could not even know whether they were being protected in accordance with the standard.

Section 6(b)(7) of the Act mandates that any standard promulgated under the Act shall, where appropriate, provide for monitoring or measuring of employee exposure in such manner as may be necessary for the protection of employees. In addition, section 8(c)(3) of the Act (29 U.S.C. 657) requires employers to promptly notify any employee who has been or is being exposed to toxic substances or harmful physical agents at levels which exceed those prescribed by an applicable occupational safety and health standard and to inform such employee of the corrective action being taken to reduce such exposures. Exposure monitoring is necessary, therefore, in order to determine whether employees are being exposed to the toxic substance at levels exceeding those prescribed by the standard and therefore should be notified as required by the Act.

In addition to the statutory requirements, there are various other reasons which make it appropriate for employers to measure employee exposure to the toxic substance.

First, employers have a legal obligation imposed by the individual standard to assure that their employees are not exposed above the permissible exposure limits. Exposure monitoring informs the employer whether that obligation is being met.

Second, if the employer determines that employee exposures exceed the permissible exposure limits, then there is an obligation (for Category I Potential Carcinogens) to institute engineering and work practice controls in order to reduce exposures to the permissible exposure levels. Hence, exposure monitoring aids in the evaluation of the effectiveness of the engineering and work practice controls and informs the employer whether additional controls need be instituted.

Third, if the permissible exposure limits are exceeded, either before or after all feasible engineering and work practice controls have been instituted, there is an obligation on the employer to provide respiratory protection for employees. The selection of a particular respirator depends largely on the level at which employees are being exposed. Therefore, exposure monitoring is necessary in order to determine whether respiratory protection is required at all, and if so, which respirator is to be selected.

The record in this proceeding provided continuing confirmation that the need for reliable exposure monitoring transcends the narrow purpose of measuring air contamination and is central to any meaningful industrial hygiene program. For example, Dr. Robert Harris testified, "when permissible exposure limits are set, monitoring programs are needed for their implementation." (Tr. 3161) The purposes of monitoring, recited above, demand that measurements be reliable and accurate. As was pointed out by Dr. Harris, decisions, especially to institute further exposure control, are not only "of substantial importance to the health of exposed workers, . . . such decisions may also involve large amounts of money. It is important that the monitoring which is done yield information which will permit the best possible decision." (Harris, S. 4)

(b) The specifics of the monitoring and measuring provision will be determined on a case by case basis. The measurements would be made by monitoring which is representative of each employee's exposure to the toxic substance over an eight-hour (8) period. They should be made without regard to the use of respiratory protection. In order to use the results of exposure monitoring to evaluate the effectiveness of the required engineering and work practice controls, to determine whether additional controls must be instituted, and to ascertain which, if any, respirator

must be used, it is important to know employee exposure levels without regard to the use of respiratory protection. Exposure measurements of each individual employee would, of course, be the best indication of each employee's exposure. However, OSHA believes that this may be too burdensome and unnecessary; therefore, monitoring which is truly representative of each employee's exposure may provide the necessary information with, in many instances, fewer samples.

Whenever there has been a production, process, control or personnel change which may result in new or additional exposures to the toxic substance or whenever the employer has any other reason to suspect an increase in employee exposure, the employer would have to repeat the required monitoring and measurements for those employees affected by such change or increase. This is important so that the employer may take the appropriate actions such as providing the appropriate respirator protection or instituting engineering controls. Standards should provide for employer notifications of each employee in writing of his exposure promptly after receipt of the results of any required measurement. Although section 8(c)(3) of the Act requires employers to promptly notify an employee who is exposed in excess of the permissible exposure limit, the standard may extend that right to employees exposed below the permissible exposure limits and establishes the time period for such notice. OSHA believes that informing employees of their exposure measurement, even below the permissible exposure limits, contributes to their understanding of their work and its attendant hazards, and the need for their attention to protective devices.

The proposed model would have always required monitoring at quarterly frequencies when employee exposure was below the permissible exposure limits, and monthly when exposures were in excess of the permissible limits. The OSHA industrial hygiene panel, NIOSH and other participants endorsed these requirements. (See St., Douglas Soule, Holaday, Billings, Tr. 2837, 2860).

Dr. Harris, Professor of Environmental Engineering, School of Public Health, University of North Carolina, testifying for OSHA endorsed "these proposed frequencies (as) reasonable" (Harris, S. 2). Dr. Harris further stated "as a practical matter, exposure monitorings at intervals more frequent than monthly are likely to take place in situations in which exposures exceed the permissible limit and where efforts are underway to implement controls. Quarterly monitoring as a minimum, has the desirable characteristic of at least one series of measurements during each season of the year, thus accommodating different comfort ventilation regimes and any seasonal changes in process or production rates" (S. 3–4) OSHA witness Holaday also endorsed quarterly monitoring as appropriate and not "particularly onerous." (Tr. 2860)

Also, the proposed monitoring frequencies were compatible with most employer testimony which showed a wide range of monitoring strategies voluntarily in use depending upon the evidence of carcinogenicity, the material and its location. For example Allied Chemical testified that for materials on a "suspect list . . . we have monitored quarterly, monthly, or semiannually" (Tr. 8531). Dr. Langer of Dow Chemical testified that his company conducted monitoring at monthly frequencies in some cases depending on "what the situation is." The kind of situation in which Dow considered monitoring less frequently than quarterly to be appropriate is "where the material has low toxicity, where the nature of the physical properties of the material are such that it would not be airborne, the process is totally contained, or where just in my judgment there is not need for frequent monitoring." (Tr. 5199)

Thus, although the hearing record provided evidence that monitoring for substances regarded as carcinogenic at the intervals proposed by OSHA was sometimes the practice of some companies, it also showed that these companies monitored at other frequencies depending upon the particular processes involved, as well as the exposure limits prescribed, and the properties of the substance.

Examples in promulgated OSHA standards also demonstrate this diversity of minimum monitoring frequencies. The asbestos standard requires semi-annual monitoring (§ 1910.1001(b)(2)(ii)). The vinyl chloride standard requires quarterly monitoring for employees exposed between the action level and the PEL (§ 1910.1017(d)(1)(ii)). Yet the standard for inorganic arsenic requires monitoring at minimum 6 month intervals for employees exposed between the action level and the PEL (§ 1910.1018(e)(3)(iii)). Therefore, while restating our belief that monitoring is appropriately performed quarterly and monthly in many circumstances, we agree with those participants who stated that the incorporation of specific frequencies in the model regulations may be inappropriate.

Monitoring frequencies, therefore, are deleted from the models in this policy. OSHA has retained, however, the format for specifying frequencies in the standards when promulgated. This is in contrast to the suggestion made by AISI (post-hearing brief at 113) that "the timing and frequency of exposure monitoring can best be left to the exercise of good industrial hygiene practice, which may dictate differing results depending on the circumstances of each individual case." Rather, we agree with API's approach that the scope and form of monitoring is appropriately considered on a substance by substance basis (API post-hearing brief at 30). AISI's approach, although meeting the objective of accommodating substances of varying forms and exposure potential, does not state any performance objectives, and thus does not constitute a meaningful standard for employers to comply with.

The issue of whether to require that initial exposure determinations be based on actual measurements, was discussed during this proceeding. One objection voiced by participants is that the initial monitoring provisions are burdensome because they become operative by the mere "presence" of a substance (see, e.g., NAM 227 p. 77). The question of what level of a substance is sufficient to activate any given provision of a standard is intended to be open to consideration in the individual standards proceedings. One reason for requiring actual measurements, rather than permitting estimates based on "paper computations," is to establish "a reference point for future monitoring." (Soule, Tr. 2837) Dr. Soule recommended initial monitoring, even in situations where the possibility of escape of the material into the environment was low. (Tr. 2837) Dr. Harris noted that "if the material is used in a process or operation one cannot determine solely from qualitative observation whether exposures are greater or less than the permissible exposure limit; measurements are necessary for this initial determination." (Harris, Tr. 2)

API suggested that the model standards permit the use of an "initial determination" (using inspections and well-accepted mathematical techniques) rather than requiring measurement in each instance (Comments of API on OSHA's Proposed Model Standards, 40). API pointed to OSHA's previous use of this approach in the Standards Completion Program and its proposals for trichloroethylene (TCE) and ketones. (40 FR 49032, 49036–37; 40 FR 20202, 20203) .

However, OSHA does not consider it appropriate to permit initial determinations rather than initial monitoring for carcinogens. OSHA believes, therefore, that in general, actual measurements provide the most reliable method of assessing the degree of employee exposure.

API had suggested that it was appropriate to require monitoring only where the substance is released as a result of work operations, to avoid requirements to monitor for ubiquitous substances such as benzene and inorganic arsenic. OSHA agrees with API, but also believes that monitoring should be required for exposures which may be generated within the workplace such as friable asbestos insulation, although they may be unrelated to work operations. In these cases, worker exposure is real, is unrelated to background contamination, is within the control of employers, and should be monitored and controlled. Such issues are best resolved in individual proceedings.

The frequency for redeterminations of exposure levels when the initial monitoring did not exceed the PEL or the action level, was also at issue. The proposal required that "additional monitoring" be conducted "whenever, there has been a production, process, control or personnel change . . . or . . . the employer has any other reason to suspect a change, which may result in new or additional exposures to (the substance)." (Proposed § 1990.160(e)(4).) Some participants considered this requirement too stringent, arguing that redeterminations should be required only where exposures are reasonably expected to exceed either the permissible levels or the limit for the respirator type used (e.g., Standard Oil, #72, p. 18). Other suggestions were for remonitoring only when there are significant changes in process or controls (e.g., #163, p. 11) or where a change is likely to result in exposure above the action level (API model standard comments at 42). However, as stated previously, the inherent variability of the air contamination in the workplace is a phenomenon independent of "any conscious change in the operation." (Harris, Tr. 3169) OSHA therefore believes that requiring additional monitoring where there has been a conscious change in process or control is appropriate. In fact, such monitoring may miss random fluctuations or those variations due to changes in process and control which the employer may not be aware of, yet will result in exposures over the PEL. To overcome this deficiency, it was suggested that remonitoring be required even if the initial determination indicates the workplace is below the action level, and no process or control change is introduced. Dr. Harris endorsed yearly frequencies for remonitoring, when the levels are very low (Tr. 3183). OSHA's industrial hygiene panel similarly agreed that even where a major process change has not taken place the concentration of an air contaminant varies from day to day and from month to month (Tr. 2856). Neither Dr. Billings nor Mr. Holaday could accept a policy for potential carcinogens which would permit no remonitoring of the workplace, even when the initial results showed exposures below the action level. (Tr. 2860). Others suggested that such a requirement would be unduly burdensome. This issue is also well-suited to regulation on a case by case basis.

Brush Wellman Inc. recommended that OSHA include provisions for specifying required monitoring devices and methods "rather than leaving them for discretionary determination by enforcement personnel." The Company argued that where, "as in the case of beryllium and probably most other materials present in the workplace atmosphere, where readings vary over time and different kinds of devices give different results," the setting of a standard based on "feasibility compliance must be accompanied by a specification of the monitoring device and program which is to be employed." (#241, at 26–27).

OSHA in certain standards has specified methods of measurements. For example, the asbestos standard (29 CFR § 1910.1001(e)) requires that "all determinations of airborne concentrations of asbestos fibers be made by the membrane filter method at 400–450 X(magnification)(4 millimeter objective) with phase contrast illumination." However, a more common and flexible approach is demonstrated by the monitoring requirement in the inorganic arsenic standard which sets specified performance objectives *viz.*, "accuracy (with a confidence level of 95 percent) of not less than plus or minus 35 percent for concentrations of inorganic arsenic greater than 5 $\mu g/m^3$ but less than 10 $\mu g/m^3$." (§ 1910.1018(e)(ii)).

OSHA believes that where, as in the case of asbestos, the available evidence showed that only one measurement method was both reliable and available, it may be prudent to require the method. However, OSHA notes that new and improved sampling and analytical methods are being developed, and that any unnecessary specification of method may inhibit their development and use.

(6) Regulated Areas (Paragraph f)

(a) There will be a provision for regulated areas for Category I carcinogens unless the Secretary explains why such a provision is inappropriate.

The primary purpose of regulated area is to identify areas where certain levels are exceeded and limit access to those areas to authorized persons. In this way, unnecessary employee exposure is eliminated.

(b) Whether there will be regulated areas for Category II Potential Carcinogens will be determined on a case by case basis.

As we have noted elsewhere, the Secretary has reserved wide latitude in the regulatory requirements for Category II Potential Carcinogens. The inclusion of requirements such as signs and labels or PELs based primarily upon the carcinogenic property of Category II Potential Carcinogens will be determined on a case by case basis. Since regulated areas are intimately tied to these provisions, whether they will be required will be determined on a case by case basis also.

(c) The details of regulated areas will be resolved on a case by case basis.

Normally, OSHA does not describe in detail the areas which must be designated as regulated areas. In some circumstances, it does (see, e.g., coke oven emissions). This issue as well as the level at which the regulated area would be established will be resolved in individual proceedings.

(7) Methods of Compliance (Paragraph g)

One of the few regulatory issues that has been definitely resolved in this rulemaking is OSHA's methods of compliance requirements, including the requirement that engineering and work practice controls be used as the primary method of complying with PEL's. As discussed more fully below, engineering and work practice controls are the only reliably effective means of protecting employees from potential occupational carcinogens. Respirators are relied on only as a means of last resort because they simply do not provide a comprehensive and reliable method of employee protection, are uncomfortable and may themselves create safety and health hazards.

This policy has been applied by OSHA in every health standard for potential carcinogens. Yet, time and again similar arguments have been made on the relative effectiveness, cost,

the need for employer discretion, and other issues. OSHA has carefully reviewed all relevant aspects of the record on this issue and concludes that substantial evidence supports the continued preference for engineering and work practice controls. Accordingly, OSHA has foreclosed further consideration of this issue except under the amendment provisions of §§ 1990.106 and 1990.145.

1. Summary of Policy. This policy and the model standard for Category I and II Potential Carcinogens restates OSHA's previously applied policy that engineering and work practice controls be used as the primary method to reduce employee exposure to or below the permissible exposure limits except to the extent that employers can establish that these controls are not feasible.

In situations where feasible engineering and work practice controls are insufficient to reduce exposure to the permissible limits they must nonetheless be used to reduce exposures to the lowest achievable level, and then be supplemented by the use of respiratory protection. In addition, a program must be established and implemented to reduce exposures to within the permissible exposure limits or to the greatest extent feasible, solely by means of engineering and work practice controls. Written plans for this program must be developed.

2. Summary of Record. Virtually all industrial hygiene experts appearing on behalf of government, industry, public interest groups and unions, affirmed the theoretical and practical superiority of engineering the contamination out of the workplace, rather than relying on respirators to filter the contamination from the worker's air supply.

OSHA's preference for engineering controls in the abstract was not seriously challenged. What was challenged was OSHA's "generic policy" of preference for engineering controls. The major objections voiced with this policy by participants in this proceeding were that the requirement, when applied to specific industry segments, specific companies, plants and operations, may prove cost-ineffective, impracticable, and otherwise economically and technologically inappropriate (see e.g. AISI, post-hearing brief; DuPont post hearing brief, NAM). It was argued that OSHA's preference for engineering and work practice controls should be left open to re-examination in each substance-specific rulemaking or be made an option for the individual employers (DuPont, API).

OSHA has scrutinized its proposed policy of preference of control strategies both to examine alternative approaches and to provide flexibility in application without eroding OSHA's long validated policy of primary reliance on engineering and work practice controls to reduce exposures to toxic materials. If the basic reasons for adopting this preference, *i.e.,* the inherent greater efficiency and reliability of engineering over personal protective controls, are no longer valid, OSHA encourages petitions to modify this policy to reflect that fundamental shift in industrial hygiene doctrine.

3. *The Reasons for the Policy.* Engineering controls with appropriate work practices are unquestionably the best method for effective and reliable control of employee exposures to cancer causing agents. Engineering controls can act on the source of the emission and eliminate or reduce employee exposure without reliance on the employee to take self-protective action. Engineering controls encompass material substitution, process or equipment redesign, process or equipment sealing, enclosure, or isolation, local exhaust ventilation, and employee isolation (e.g., a standby pulpit, as opposed to personal protective equipment). Once engineering controls are implemented, the employee is permanently protected, subject only, in some cases, to periodic preventive maintenance.

The record contains numerous references to effective engineering solutions to controlling exposure to highly toxic substances. Examples of process or equipment modification include shifts in reaction chemistry which have avoided the production of by-product BCME in product CCME. Also, conversion from spray painting to a paint dipping operation has successfully reduced the amount of atomized paint droplets in the workplace. Seals have been highly effective. Metallurgical purification processes which rely on hydrometallurgy rather than pyrometallurgy can be sealed so as to prevent exposures (Tr. p. 2756–7). The use of double mechanical equipment seals which are internally pressurized with an inert pressurizing fluid at a greater pressure than is in the process itself seals hazardous materials even when equipment failure occurs. The use of alarms to detect such leaks permits their timely repair. Maintenance of ventilation ductwork and pneumatic transfer systems under "negative pressure" (i.e., less than ambient pressure) similarly seals leaks of hazardous materials.

Examples of process isolation or enclosure include special automated sand blasting cabinets designed to completely enclose the operation and prevent the escape of silicous dust, spray painting enclosures housing automatic painting equipment, and glove box facilities for handling carcinogens pharmaceuticals, biological agent and radioactive isotopes (Soule, S. 11, Billings, S. 9).

Local ventilation (usually combined with partial to complete enclosure) is a commonly used control method (Soule, p. 11). It is applied most effectively in capturing emissions at the point of potential introduction to the workplace. The use of temporary enclosures and movable ventilation ducts can make local ventilation extremely versatile (Holaday, p. 4). Local ventilation is commonly and effectively applied in preventing workplace emissions from sources such as product stream sampling stations, pump gland seals, agitator shaft seals, and valve stem packings (Billings, S. p. 9). In vinyl chloride operations, local ventilation is used as a backup engineering control to prevent emissions in the event that the primary engineering control technique (process sealing) fails, thus giving a higher degree of confidence to the control system.

OSHA notes that the record of this and other rulemakings indicates that local ventilation may best serve as an adjunct to other engineering control measures, rather than the primary control strategy. OSHA witness Billings stated that ventilation controls "may be less desirable than complete control at the source by elimination or process enclosure." (S. 8–9) Similarly, Soule testified "after a particular piece of equipment or process has been enclosed to the maximum extent, ventilation should be used to control any contaminant that might otherwise escape into the work environment." (S. 11)

However, OSHA has determined not to establish a preference for certain types of engineering control over other types of engineering controls for the following reasons. First, OSHA's primary concern is that the PEL is met through the use of engineering and work practice controls. Compliance may be achieved through the use of ventilation and other engineering controls. Further, the testimony of this record indicates that local ventilation is generally utilized appropriately. Its limitations are obvious, and the increasing need to design ventilation systems to meet EPA ambient air restrictions increases the cost of these systems and is a disincentive to their appropriate use. It should be noted that the environmental

impact of standards issued under the policy will be considered, and that the environmental impact of particular engineering controls may be raised.

Further advantages of the above strategy are the benefits in terms of easier compliance with environmental pollution control regulations which may be promulgated by the Environmental Protection Agency and otherwise limiting contamination of the general environment.

Exhaust of contaminated air or gas is restricted by environmental quality concerns. Cleaning of exhaust gases may be necessary, which requires energy and capital resources, thereby making ventilation less desirable than complete control at the source by elimination or process enclosure (Billings S. 8). Mr. Holaday pointed out that engineering controls limit the spread of contamination to other portions of the plant, and to surrounding environs (Tr. 2798).

Other benefits may derive from the implementation of engineering controls. Examples given are "improved general housekeeping, economic recovery of collected material and possible reuse, reduction in general ventilation requirements, and improved quality of the product by minimizing cross contamination." (Soule, p. 11, testimony.)

"Work practice controls" or "work practices" accomplish the same results as engineering controls, but rely upon employees to repeatedly perform certain activities in a specified manner so that airborne concentrations are eliminated or reduced. Work practices may involve simple instructions to employees to keep lids on containers, to clean up spills immediately, or to observe required hygiene practices. Good work practices are often required in conjunction with engineering controls; for example, where employees perform an operation under an exhaust hood, they must perform their work in such a way as to maximize the efficiency of the ventilation equipment.

Work practices do not include administrative controls. The term administrative controls refers mainly to employee rotation, so that for any one employee his exposure is lower or his work hours are reduced. Although OSHA's recently promulgated lead standard included administrative controls in its definition of work practices, the preamble to that standard (43 FR 52990) made it clear that since administrative controls, by definition, expose more employees to the contaminant, they are unacceptable when the contaminant is one for which "no effect" levels are unknown, such as carcinogens. *Ibid.*

Work practices also act on the source of the emission but rely upon employee behavior, which in turn relies upon supervision, motivation and education to make them effective. For this reason work practices are not as desirable a method as engineering controls. But because the two methods often must be employed together to make either one effective and because they are the only methods that act to eliminate or reduce the hazard at its source, they have been given equal status in the compliance priorities of the final cancer policy.

4. *The Record as a Whole Supports the Policy.* The rulemaking record in the "cancer policy" generated substantial support for the use of engineering and work practice controls as the preferred means of preventing employee exposure, both from government and industry witnesses. The basis for this priority has been previously stated in Appendix A to OSHA's Regulatory Analysis of the proposal, and the preamble to the recent OSHA standards on inorganic arsenic (43 FR 19584, 19617–19618), lead, DBCP and acrylonitrile (43 FR 45800), among other places.

As has been pointed out in these documents, respirators are the least satisfactory means of control because of difficulties inherent in their design and use. Respirators are capable of providing good protection only if they are properly selected for the types and concentrations of airborne contaminants present, properly fitted and refitted to the employee, worn by the employee, and replaced when they have ceased to provide protection. While it is theoretically possible for all of these conditions to be met, it is more often the case that they are not. Consequently, the protection of employees by respirators is not very effective and is therefore permitted only in certain specified circumstances. For example, proper facial fit is essential, but due to variation in individual facial dimensions, and the limited range of facepiece configurations, such fit is difficult to achieve. Often the work involved is strenuous and the increased breathing resistance of the respirator reduces their acceptability to employees. Safety problems presented by respirators must also be considered. Respirators limit vision. Speech is also limited. Voice transmission through a respirator can be difficult, annoying and fatiguing. Movement of the jaw in speaking also causes leakage. Communication may make the difference between a safe, efficient operation, on the one hand, and confusion and panic, especially in difficult and dangerous jobs, on the other hand. Also skin irritation can result from wearing a respirator in hot, humid conditions and such irritation can cause considerable distress and disrupt work schedules. The extent of this problem is even greater where the toxic substance is a skin irritant and becomes trapped between the respirator facepiece and the skin.

It is clear therefore that respirators cannot be considered as the primary means of employee health protection. Nevertheless, they do provide some protection and OSHA has concluded therefore that under certain circumstances, the employees must use the respirators provided. Many witnesses support this view (see e.g. Held and Douglas).

OSHA witness Bruce Held recommended against respirators as the first line of defense on the basis that:

> ". . . engineering controls are positive. You know if a ventilation system breaks down; when it happens you will have one or two trained engineers or maintenance people that can take care of it; in the meantime you can evaluate your people. On the other hand, you do not know a respirator leaks until after the man becomes sick" (2785).

He fairly summarized the OSHA position as follows:

> "I feel very strongly that (the use of respirators) is the second line of defense and that engineering controls are by far the most effective and preferred method." (Tr. 2683)

This position was also supported by industrial hygienists of recognized expertise in industry. For example, Dr. Sowinski of Uniroyal testified that "we adhere to the basic requirements of good industrial hygiene practice, that engineering controls are the best choice." AIHC too "agree[s] that engineering controls should be considered first." (Tr. 8399) Dr. Langner of Dow (Tr. 5118) and Dr. Strassburge of BF Goodrich, among others, also concurred with this position.

Dr. Karrh of DuPont stated that "you would much prefer to have whatever the offending substance is controlled at its source." (Tr. 5365) Other industry witnesses support the superiority of engineering controls and the weaknesses of personal protection (Dr. Thorpe, API, Tr. 4514–16, Dr. First, API, Tr. 6853, Casey, G. E., Tr. 7905, Janus, Hooker, Tr. 4162).

In spite of the general concurrence among knowledgable health professionals concerning the primacy of engineering and work practice controls over personal protective equipment, a few commenters stated that toxic substances should be controlled through

personal protective equipment rather than through engineering controls. Representative comments were:

"Toxic substances in the workplace should be reduced through personal protective equipment rather than through mandated engineering controls." (250–7)

"If adequate surveillance is maintained, the use of personal protective equipment is an effective control measure. An employer should be given the option of establishing a personal protection equipment program and/or work practices control program to minimize the employee's exposure as long as they are equally or more effective than programs based on engineering controls." American Telephone and Telegraph Co. (To same effect, see, e.g., #210, p. 12; FMC Corp. #818).

Another representative comment stated:

"Engineering controls . . . would probably require large dollar expenditures in the form of capital investment and operating expenses . . . OSHA should take into consideration any combination of equipment controls, engineering controls, work practices or personal protective equipment that adequately shields the worker from known or potential carcinogenic substances, rather than legislating engineering controls as the sole protective remedy" (see also #282, p. 7; #208, p. 10).

The above comments are representative of numerous statements in the record. These statements share a number of misunderstandings, as discussed below:

(1) The assumption that personal protection can be as effective as engineering controls is not supportable. No example is given in the hearing record which describes a specific case in which protective equipment is as effective as engineering controls in preventing or providing equivalent reduction in worker exposure. This is due to the *intrinsic limitations* of respirators compared to engineering controls. OSHA feels that these limitations are such that a control strategy which relies on protective equipment as a primary means of protection cannot be made as effective as a strategy which relies on reductions of emissions at their source as a first line of defense, with personal protection as a backup.

(2) The assumption that personal protective equipment would not continue to play an important role as a second line of defense after the installation of feasible engineering and work practice controls, thus depriving the employer of needed flexibility in devising an overall control strategy, is a misunderstanding of OSHA's intent. OSHA strongly supports the implementation of the most effective personal protective equipment program that is possible, after the implementation of all feasible engineering controls.

(3) The assumption that reliance on engineering controls deprives the employer of necessary flexibility in developing a control strategy exhibits a misunderstanding of the alternative control technology possibilities. There are usually many effective engineering alternatives for solving a given problem. One example of this involves control of the exposures associated with manual cleaning of residual polymer which builds up on the inside of PVC polymerization reactors. Alternative control measures have included:

—automated cleaning using high pressure water spray equipment

—automated cleaning using a chemical solvent system

—steam vacuum stripping to remove residual monomer prior to cleaning

—use of coatings on the reactor walls which substantially reduce the rate of polymer buildup and hence the frequency of cleaning

—use of additives to the reacting mix which modify the reaction so as to reduce buildup on the reactor walls

—use of different process technology (bulk polymerization) which avoids the problems associated with a three phase water-solid-monomer mix, resulting in substantial reduction in polymer buildup on reactor walls.

—use of much larger reactors with a much higher volume-to-surface-area ratio, which greatly increases production quantity in relation to the frequency of required reactor cleaning

As stated previously, engineering controls may include material substitution, process or equipment redesign, sealing, enclosure, isolation, local exhaust ventilation, and employee isolation. This range of control options provides ample opportunity for American industry to exercise its demonstrated innovativeness.

A second group of comments from participants in the rulemaking raises the concern that the OSHA policy of reliance on engineering controls will place an intolerable economic burden on industry. For example, it was stated that the proposal allowing exposure reduction only by engineering and work practice controls, rather than by use of employee protective equipment, is unduly burdensome and probably will result in making it economically infeasible to manufacture many products in the United States and yet remain competitive with foreign-produced products. (242 at 4) It was also stated that mandating engineering controls rather than personal protective equipment will cause severe hardship, especially in cases of small businesses (see 135 at 3.).

These comments also indicate misunderstanding of the proposed model standard. The proposal had stated that "the permissible exposure limits for Category I toxic substances are not chosen as 'safe' or 'no-effect' levels, but on the basis of OSHA's belief as to the lowest feasible levels. OSHA is mandated by the Act to consider feasibility in setting regulations." (p. 54181)

Recent OSHA rulemakings such as acrylonitrile and cotton dust have involved extensive discussions of feasibility. Additional discussion is included in this preamble. OSHA has incorporated a variety of contingencies (including delayed compliance times) in these rulemakings in order to allow for feasibility constraints. OSHA has consistently and clearly expressed its intention to include feasibility as a determining factor in the permissible exposure level setting which will occur in individual rulemakings.

Other comments had called for exceptions to be made in the required use of engineering controls for cases where exposures are intermittent, are limited in time, or are limited to a small number of employees.

For example, it was argued that personal protective equipment in conjunction with work practice controls would adequately protect the small number of workers exposed to small batches of a substance for short time periods; and that an employer should not have to place total reliance on engineering controls to protect one or two employees from intermittent exposure. (Notice #90 p. 18 Republic Steel).

Relatedly, API contended that certain engineering or work practice controls will be "cost-ineffective in certain situations even though they are technologically and financially possible." API's examples are "(1) work operations where the PEL's are exceeded only briefly or intermittently and (ii) work operations where engineering or work practice controls are enormously expensive, yet will accomplish only a minor reduction in exposures, so that respirators will be required in any event." (Comments of API on OSHA's Proposed Model Standards at 48).

AISI indicated that its concern was with "mobile employees who move from place to place and areas in which one man would be involved once a week to look at one dial in a pump room, and that is it; and if you went into engineering controls the amount of

money may be astronomical to provide the controls" (Tr. 4712–4713).

OSHA agrees that both the cost of installing engineering controls and the number of employees protected by such controls may vary substantially from case to case. Previous discussions have presented the *inherent* advantages of engineering controls over personal protection, which apply in virtually *all* cases. As stated previously, OSHA has concluded that this is not an issue of serious debate among knowledgeable health professionals today.

The hearing record does not contain good examples of employee exposure situations in which a few employees would require protection by enormously expensive engineering controls. In the case cited above by AISI, for example, the pumproom dial may be replaced by a commonplace and relatively inexpensive device which senses the pressure, temperature, flow rate, etc. (as appropriate) and transmits this signal to an environmentally-regulated control room, thus avoiding the need for employee entry into the pump room. This is an example of process isolation through automation/remote control, which is one of numerous recognized engineering control methods. During the hearing API again suggested that in certain work place circumstances respirators should be used as the first line of defense. OSHA's industrial hygiene witnesses agreed that in certain obvious circumstances respirator use was appropriate. These circumstances were described as "before one could put in engineering controls", "when the engineering control is not operating"; "in emergency situations"; and "if you have the engineering controls installed, and they are good, but they are not good enough." OSHA standard notes that the proposed and final model would permit respirator use in these conditions.

In addition, API posed certain hypothetical conditions of workers exposed temporarily during the work day, "where respirators might make good sense and provide appropriate levels of protection." One such situation was a highly automated workplace with a worker operating primarily from a control room, where he is protected by engineering controls, but where several times a day where for 15 minutes the worker enters the process room and is exposed to an unspecified level of contamination. The assumed cost of engineering controls in the enclosed process room is millions of dollars (Tr. 2775–2776). OSHA witness Held stated from the "context of feasibility," looking "at the money involved . . ." talking about millions of dollars for one person in a fifteen minute exposure . . . that very possibly in that particular situation it would make more sense to use the respiratory protection." (Tr. 2776). OSHA witness Douglas, however, pointed out that the frequency of entry into the automated area should be considered in determining whether engineering controls should be installed to protect employees entering the automated area." (Tr. 2776). API described another hypothetical situation—"a truck driver whose only potential exposure is at time of loading which might be twice a day," and suggested control using respirators (Tr. 2777). OSHA witnesses Held and Douglas testified that other variables such as whether "there are clouds of material" being dispersed, the potential exposure of other people, and the number of trucks a day being loaded should be considered before respirator use could be permitted as a first line of defense. Thus, neither respirator expert testified that respirators would be more effective; and both pointed out that the superficially minimal exposure situations suggested by API as candidates for primary control by respirators must be scrutinized for wider, higher or more frequent exposure potential which would disqualify the use of respirators as a primary control.

As indicated by the small number of specific examples provided in the hearing record, OSHA believes that the number of exposure problems which will not be amenable to solution by engineering control measures will not be great. Nonetheless, the cancer policy, including OSHA's enforcement policy of considering feasibility in an individual case, may consider the infrequent exposure situation where a partial reliance on protective equipment may be an effective control approach.

The proposed model standard had stated that respirators may be used as the primary control strategy in work operations such as maintenance or repair activities in which the employer establishes that engineering and work practice controls are not feasible, or as a supplemental control strategy "in work situations where feasible engineering and work practice controls are not yet sufficient to reduce exposure to or below the permissible exposure limits."

OSHA's reasons for specifying repair and maintenance activities in the proposed provision were that they are intermittent, often unpredictable, and often undertaken when engineering controls break down. Under such circumstances it is likely that respiratory protection often will provide effective protection to these exposed employees, because, for example, when exposure durations are short, many problems associated with respirator use, such as discomfort, decrease in productivity, loosening of face seals and saturation of filter beds, either will not occur or will be of very minor significance.

In the final regulation OSHA has deleted the specific mention of repair and maintenance activities, as an illustration of "work operations . . . in which engineering and work practice controls are not feasible." The record pointed out, and OSHA agrees, that some maintenance and repair activities are feasibly controlled by engineering and work practice controls (Tr. 2684–2685). Therefore, in order to clarify that OSHA did not intend to exclude maintenance and repair operations from its general policy of requiring primary reliance on feasible engineering and work practice controls, OSHA has made the above described changes in the final model standard.

This final policy, like the proposal, provides that where feasible engineering and work practice controls are insufficient to reduce exposure to the permissible limit, they must nonetheless be used to reduce exposure to the lowest achievable level and then be supplemented by the use of respiratory protection. This policy is not new to this Cancer Policy rulemaking. Virtually all OSHA health standards have applied this policy. See, for example, the lead standard, § 1910.1025(f)(1)(ii); the arsenic standard, § 1910.1018(h)(1)(iii) and the vinyl chloride standard, § 1910.1017(f)(2). The reasons for requiring the installation of feasible engineering and work practice controls, even when insufficient to reduce exposures to the PEL, was explained in the inorganic arsenic preamble as follows: "Even in situations in which engineering controls will not succeed in reducing exposure levels below the TWA limit, it is still appropriate to require all feasible engineering controls, even though it was necessary for supplemental use of respiratory protection. Engineering controls, by minimizing the exposure, without regard to the use of respirators, will have minimized the potential for overexposure resulting from poorly fitting respirators and will usually reduce the number of employees who need to wear respirators. (43 FR 19617). The preamble to the coke oven standard also discussed the reasons for implementing such a requirement. There, OSHA stated:

OSHA believes that the most effective means of controlling employee exposures is

to contain the emissions at their source. We do not believe the use of respirators is an acceptable long term solution to the hazards associated with exposure to coke oven emissions because of the many drawbacks relating to their use. (See discussion under Respirators below).

A necessary element of this approach is to require the use of engineering and work practice controls which can be implemented to reduce employee exposures to the lowest level achievable by these controls, even when these controls may not reduce exposures to or below the permissible exposure limit. In reaching this conclusion, we have carefully considered the possibility of requiring such controls only where there is a reasonable expectation that exposures would be reduced to or below the permissible exposure limit. In this regard, it should be noted that there is no known safe level of exposure to coke oven emissions.

We fully expect respirators to be approved by NIOSH for coke oven emissions in the near future. However, we still would not know each employee's actual intake of coke oven emissions because of variability in quality control, fit, the extent to which supervisors enforce the requirement that employees wear respirators, etc. Therefore, since reduced ambient air levels necessarily reduce actual employee intake, there is a greater likelihood that actual employee intake will be at or below the permissible exposure limit as a result of the installation of such controls.

In addition, it is difficult if not impossible to predict in advance the levels which will be achieved by implementing particular engineering and work practice controls. Therefore, there may be instances where employers are able to achieve lower levels than they had anticipated. Finally, requiring employers to implement controls only where they expect to reach the permissible exposure limit with such controls would provide an incentive to employers to conservatively estimate the effectiveness of controls, and could divert attention from reducing exposures to establishing that particular controls would not reduce exposure to or below the permissible exposure limit. In these circumstances, particularly noting the goal of compliance with the permissible exposure limit solely by means of engineering and work practice controls, we have concluded that it is necessary to require employers to reduce levels by means of engineering and work practice controls which can be implemented to the lowest level achievable by these controls, even when such controls are not sufficient to reduce levels to or below the permissible exposure limit. (41 FR 46759)

OSHA expert witness Duncan Holaday testified similarly that there are "reasons for putting in engineering controls even though they are not as effective as it was hoped they would be . . . You reduce the contamination in the work room air . . . You also limit the spread of contamination to other portions of the plant and to the surrounding environs." (Tr. 2798). OSHA witness Douglas also endorsed requiring engineering controls to be utilized to the greatest extent feasible, then supplemented by respirator use. "The engineering controls will reduce the number of employees on respirators. The lower exposure levels resulting from the engineering controls will permit the use of simple, less confining and easier to use respirators." In addition, such reductions in exposure may also reduce the amount of time employees will need to wear a respirator. Finally, lower background levels will reduce the potential exposure for those employees who have not been properly fitted to their respirator or who do not wear them conscientiously.

Only a few commenters stated that OSHA's proposed priority for controls ignored "the requirement that OSHA take economic feasibility into account" in setting standards (see, e.g., #252) OSHA required methods of compliance set out in the proposal and the final model standard explicitly state that engineering and work practice controls are required to be used to reduce employee exposure to the PEL, "except to the extent that the employer establishes that such controls are not feasible." Similarly, proposed § 1990.160(g)(h)(ii), which sets out the conditions under which respirators may be used, explicitly mentions feasibility. Further, as discussed in detail elsewhere, in subsequent rulemakings undertaken pursuant to this policy, OSHA will be bound by the requirements of feasibility in establishing standards.

As noted above, OSHA rulemakings such as acrylonitrile, cotton dust and lead have involved extensive discussions of feasibility. OSHA has incorporated a variety of contingencies (including delayed compliance times of up to ten years for primary lead smelters, for example) in these rulemakings in order to allow for feasibility constraints. The continued usefulness of these approaches in future standard settings is anticipated. Since their application must accommodate the financial and technological conditions of the affected industry, OSHA will consider on a case-by-case basis appropriate compliance periods for specific industries.

There will be a provision which requires employers to develop a written compliance plan in order to meet the PEL primarily through engineering and work practice controls, unless the Secretary explains why such a provision is inappropriate. The need for a compliance plan is clear; a written compliance plan is a necessary prerequisite to rationally planning a control strategy. In addition, it is an objective check to see if employers are taking the initial steps towards compliance with standards. There was substantial support for this provision (see, e.g., Dr. Billings). The details of compliance plans will be resolved on a case-by-case basis.

8. Respirators (Paragraph h)

Respirators will be required as a secondary means of compliance in certain circumstances in order to comply with any PELs established under the Policy.

The general need for provisions which would be applied when respirators are used to protect employees against airborne contamination from potential carcinogens is supported by this Cancer Policy record and other relevant rulemaking records.

The need for effective requirements for respirator use in standards subject to the policy is an important supplement to engineering and workpractice controls. First, conditions where respirators must be used are acknowledged and specified in the model standard. These circumstances are: (i) during the time period necessary to install or implement feasible engineering and work practice controls; (ii) in work operations in which engineering and work practice controls are not feasible; (iii) in work operations where feasible engineering and work practice controls are not sufficient to reduce exposures to or below the permissible exposure limits; and (iv) in emergencies.

As noted in the discussion on methods of compliance, the inherent limitations of respirator design and use render them the least preferred control strategy. OSHA acknowledges, however, that where they must be used, such as when more preferred controls have not or cannot be installed, it is necessary to minimize their limitations by insisting on careful selection, use and fit. These elements are included in the respirator provision in the model standard.

OSHA explained its proposed model respirator provisions as follows:

The three model standards require that the employee be properly trained to wear the respirator, to know why the respirator is needed and to understand the limitations of the respirator. An understanding of the hazards involved is necessary to enable the employee to take steps for his or her own protection. The respiratory protection program implemented by the employer must conform to the program set forth in 29 CFR 1910.134. This section contains basic requirements for proper selection, use, cleaning, and maintenance of respirators.

The three proposed model standards also contain a respirator selection table (Table I) so the employer will be informed of and provide the type of respirator which affords

the proper degree of protection based on the airborne concentrations of the toxic substance.

To prevent skin irritation and to minimize the discomfort of respirator use, the three model standards require that employees must be allowed to periodically wash their faces and respirator facepieces in order to remove any accumulation of the toxic substance or to reduce the chance of irritation from the wearing of the facepiece itself, such as a heat rash.

In the Cancer Policy proceeding, participants questioned the deletion of a quantitative fit test requirement from the models. OSHA had not included such a requirement because the Agency believed the necessary equipment was neither widely available nor feasible (Wrenn, Tr. 94).

Witnesses with expertise in respirator protection endorsed the greater reliability of quantitative fit testing although they did not consider that such a requirement should be mandatory (Held, Tr. 2675–76, Douglas Stmt.). Qualitative fit testing is still considered reliable if done "extremely carefully," and some experts recommend that a greater protection factor be allowed in such case (Id). The final model includes a requirement that the employer assure that respirators fit properly.

OSHA notes both the theoretical superiority of quantitative fit testing and the potential feasibility problems of quantitative fit testing for all industries. Determinations on these issues must await the development of a relevant factual record in each rulemaking.

9. Protective Clothing and Equipment (Paragraph j)

(a) There will be a provision for protective clothing and equipment, unless the Secretary explains why such a provision is inappropriate.

Generally, there was little debate in the rulemaking record concerning the reasonableness in a general sense of requiring "appropriate" personal protective clothing and equipment. Duncan Holaday, testifying for OSHA, gave the most complete explanation of the reasons for this requirement:

> The appropriate use of personal protective clothing, gloves and goggles is an essential part of an effective program for minimizing exposure to occupational carcinogens. Obviously, choice of clothing and equipment should depend on the degree of protection desired and the form of the substance encountered. For example, during my tenure with the public health service, I inspected oil refineries whose employees had shown a historic excess of skin cancers attributable to exposure to pyrolysis oils. Although truly impervious clothing is often restricting to the wearer and uncomfortable, I observed that the oil industry provided and employees wore impervious clothing to protect against contact with this substance. The work operations presenting the risk of exposure were short enough so the significant discomfort of the clothing was not a disincentive to its use. In addition, the obvious hazard of skin cancer overcame any inconvenience of wearing impervious clothing in the oil refineries.

In addition to minimizing the cancer hazard from contact with the substance, protective clothing prevents skin absorption of potential occupational carcinogens.

As noted elsewhere, the appropriate protective clothing and equipment must be provided by the employer at no cost to the employee.

(b) The detailed requirements of the protective clothing and equipment provisions will be determined on a case-by-case basis.

The type of clothing and equipment, the circumstances which trigger the requirement, the cleaning and disposal of them and other provisions will be determined on a case-by-case basis pursuant to this policy (See, e.g., AISI's suggestion that each substance should be evaluated as to its physical and chemical properties before mandating specific requirements on protective clothing and equipment).

10. Housekeeping (Paragraph k)

There will be a provision which requires a housekeeping program to minimize accumulations, unless the Secretary explains why such a provision is inappropriate.

The rulemaking generated substantial discussion concerning the proposed model standard's requirement relating to housekeeping. In its preamble to the proposal, OSHA set forth the reasons for its requirements as follows:

> Removal and prevention of accumulations of the toxic substance dust and liquid deposits on all surfaces in the workplace are important aspects in minimizing employee exposure, particularly in the case of a Category II toxic substance where there may not be a mandatory reduction in the present permissible exposure limits, per se. To assure that the toxic substance is not reintroduced into the workplace air, all three model standards prohibit dry sweeping or the use of compressed air for cleaning of floors and other surfaces where the toxic substance dust or liquid deposits are found.
>
> As important, all three models standards require that when the toxic substance is present in a liquid form, or as a resultant vapor, that all containers or vessels shall be enclosed to the maximum extent feasible and tightly covered when not in use.

The final model standard covering housekeeping is substantially different from the proposal. It imposes a general obligation on employers to adopt a housekeeping program to minimize accumulations of the substance. The detailed housekeeping techniques in the proposed provision, although useful and appropriate in many situations, are being deleted as inappropriate for promulgation as policy statements of the agency.

Mr. Soule, testifying for OSHA, enlarged on the objectives served by housekeeping provisions as follows:

> There are really two objectives to these provisions: one to prevent accumulation to the point where there is a reasonable chance or opportunity for secondary dispersal of the contaminant into the environment; and the second objective to maintain levels to such a point where any inadvertent or otherwise direct contact, let us say with the skin, would prevent a significant opportunity again for exposure by that route, by skin absorption. (Tr. 2628).

The question of how to measure surface contamination was addressed by some participants. Dr. First, testifying for API, pointed out that uniform sampling procedures for "wipe tests" are required to get consistent and reproducible results. Some variables in sampling procedure would be the area sampled, the force used in wiping, and the number of "wipes". (Tr. 6856). Dr. First also raised the question of how to interpret the data obtained from "wipe tests", especially where the health hazard is only known to result from inhalation (Tr. 6856). Dr. Peterson, testifying for PMA, described techniques for assessing surface contamination, and indicated that "surface contamination is not a well-developed art; it is something that has been sadly neglected." (Tr. 7081–7082). In some cases the available techniques are not substance-specific (Tr. 7081). Both Drs. First and Peterson stated that wipe sampling has been used most extensively for radioactive materials (Tr. 7083). OSHA therefore believes that the feasibility as well as the appropriateness of wipe testing should be assessed in substance-specific rulemakings.

Although there was agreement that the "free of accumulation" provision was appropriate when "necessary", there was disagreement about when the provision was necessary.

For example, a representative of the plastics industy testified that "requirements for cleaning surfaces are not appropriate for materials which have low volatility, but which are not absorbed through the skin." (Tr. 6698). OSHA therefore has deleted this proposed provision. Instead, cleaning of surfaces is included in the list of housekeeping operations which the employer should periodically perform. The extent of cleaning for all operations depends upon what is appropriate and

necessary to prevent significant skin and eye contact and ingestion. OSHA does not intend to establish a no contact compliance standard by these provisions.

Housekeeping is expected to remain the employer's most obvious and inexpensive method of reducing exposures.

The record shows general support for the concept of good housekeeping. The programs of specific industries and employers vary considerably. Some employee testimony indicated that housekeeping programs were casualties of increased productivity programs, resulting in eliminating the people who cleaned things up (Tr. 6265).

Examples of company housekeeping programs are part of the rulemaking record. For example, Robert A. Hoffer, President of Hoffer Plastics, employing 380 persons testified that his company has "regular housekeeping inspections on a weekly basis" (Tr. 6718). It was pointed out that smaller companies may have to rely on their production people to do the cleanup, whereas larger companies can hire crews to clean up specifically (Tr. 6719–20).

Industry participants pointed out that good housekeeping in production areas serves other interests, such as providing products for an American market which will be clean and free of contamination. (Tr. 6717–6718). Sometimes, contamination of a product is cause for customer rejection (Tr. 6723).

11. Waste Disposal (Paragraph l)

There will be a provision prohibiting dispersion of carcinogenic waste material into the workplace, unless the Secretary explains why such a provision is inappropriate.

The proposed model standards would have required that employers dispose of waste, scrap, equipment or debris containing the toxic substance by collecting and disposing of it in sealed bags or other closed containers to prevent dispersion of the toxic substance outside the container.

The final model standard has changed the focus of the requirement from a specific practice to a performance requirement of preventing dispersion of the carcinogenic waste material into the workplace environment. Of course, in many cases, sealed containers will be used to meet this requirement. Also, OSHA recognizes that the dangers of contamination from carcinogenic wastes extends to future employees of the on-site disposing employer or of his successor, to employees of employers whose facilities are utilized for disposal, such as landfills or garbage dumps, and to employees who may contact the hazardous wastes at those facilities, such as employees engaged in construction on such a landfill. Therefore, the model standards also indicate that, where appropriate, employers should label, or otherwise inform all employees who may foreseeably contact the waste material, of the identity of the material. In most cases, where disposal is effected by placing the liquid or solid waste material in containers, a label, designed to withstand the conditions of disposal for the foreseeable period of employee contact, will be an appropriate way to comply with this requirement. The method of informing employees can be coordinated with any other requirements set by federal agencies such as EPA, or state or local governmental bodies exercising authority over waste disposal.

OSHA acknowledges, as was pointed out by NRDC, that the proposal "makes no provision concerning how or where to dispose of contaminated wastes." (#145 at 56). The final model standards similarly omit such specific provisions. As with the other model provisions, OSHA believes that the diversity of substances, industries and plants reasonably precludes dictating specific waste disposal procedures in this generic regulation. Consideration of this issue is best left to individual rulemaking proceedings or as part of OSHA's assessment of environmental impact.

12. Hygiene Facilities and Practices (Paragraph m)

There will be a provision for hygiene facilities and practices for Category I Potential Carcinogens unless the Secretary explains why such a provision is inappropriate. The inclusion of a requirement to provide hygiene facilities for a Potential Category II Carcinogen is discretionary and will depend on the circumstances of the substance, its use, and affected workplaces. It is first intended that certain facilities covered by 29 CFR 1910.141, *i.e.,* showers and change rooms, be included when they are appropriate, given the properties of the substance, the form of exposure, and the work operations involved. OSHA intends that the details of the standards promulgated under the cancer policy will be open in each individual rulemaking. To extend the supported rulemaking record in each case, requirements may differ in details from those in § 1910.141. In addition, the proposal had also stated that where food was consumed at the workplace, lunchrooms with a filtered air supply will be provided.

The general reason for requiring such kinds of facilities is to protect employees from secondary contamination from the regulated substance, either via their own body and clothing, or their fellow workers. Witnesses acknowledged during the cancer policy proceedings the value of these requirements. For example, Mr. Soule testified, "provisions for 'clean' and 'dirty' locker areas for street and work clothes, respectively, use of shower or other personal hygiene facilities . . . all can be considered work practice controls, equal in importance to the engineering controls mentioned earlier". (S. 13) (See also testimony of Mr. Holaday, Dr. Billings and Mr. Douglas). In other recently promulgated OSHA standards, OSHA has required that employees shower at the end of a shift (See, e.g., § 1910.1018(m)(2)(i), inorganic arsenic; § 1910.1029(i)(2)(i), coke oven emissions; § 1910.1044(1)(2)(i)) and wash or shower immediately after significant contamination, in some cases (e.g., 1910.1044(1)(2)(ii), DBCP).

The proposal specifically required that employers assure that employees shower at the end of the work shift. Showering was generally agreed on as valuable employee protection, when appropriate to the properties of the substance and working conditions. Industry witnesses testified that showering after contact with some forms of carcinogenic contamination was appropriate, and in their own companies required showering after contact. (See, e.g., Upjohn #163, appendix p. 2) Mr. Lynch of Exxon testified that showers would be necessary and definitely should be required when "it is possible to have significant skin contact to substances which can either cause skin cancer or enter the body through skin . . . on the other hand, for a gas, for example, that does not cause skin cancer and cannot enter through the skin, showers are not needed". Thus, whether and when showering should be required are issues particularly suited for substance-specific rulemaking.

Requirements for change rooms have also been incorporated in standards covering toxic substances, especially when they are in dust or particulate form. (e.g. § 1910.1001(d)(4) asbestos; § 1910.1018(m)(i) inorganic arsenic; § 1990.1029(i)(1) coke oven emissions.).

The necessity for change rooms is related to the employer's obligation to provide protective clothing and equipment. The primary purpose of protective clothing and equipment is to serve as a barrier between the employee and the contaminant. Without change

rooms to remove and dispose of contaminated clothing and equipment, they would become the carriers of contamination they were designed to avoid.

OSHA was surprised that its proposed requirement relating to lunchrooms engendered significant debate. It appears that the preamble to the proposal (42 FR 5417) may have been misunderstood. OSHA's intention was not to require that employers provide lunchrooms, but rather, that employers assure that the areas in the work place in which employees eat their lunch are relatively free of contamination and that any such areas be comfortable so as to encourage employee use. Indeed, Dr. Melvin First, who testified for API, agreed "that the lunchroom should be tempered, whether the air has to be cooled or warmed or whatever. It should be a comfortable place to eat." (Tr. 6868.) The record indicates that some companies routinely provided this (e.g., Allied Chemical Tr. 7440).

Other industry support for tempering lunchroom air turned on the degree of contamination in the vicinity of the lunchroom. For instance, M. Janes of AISI supported the requirement when it is located "where people eat near the substance in question", but objected to the requirement when the lunchroom is located "half a mile away". (Tr. 4171.) OSHA has retained the guideline, but added the words "if appropriate" to indicate that the need for such a provision should be determined on a case-by-case basis.

The degree of exposure which should "trigger" the various requirements included in the hygiene provisions was at issue. OSHA rejects the suggestion of API that the model standards should provide that "the hygiene facilities are required only for workers exposed above the PELs, not to all workers exposed to airborne concentrations of a substance". (Comments on Model Standards, 53, for 76.) Where, as here, the requirements are intended to reduce exposure via all routes, OSHA believes it does not make sense to "trigger" the requirements at a permissible exposure limit based on airborne concentrations alone. Additionally, as discussed earlier, the PELs are established based on feasibility, not on a determination of a "safe" exposure level.

Another issue was raised concerning OSHA's guideline that employers "assure" the use by employees of prescribed hygiene facilities.

The use of the word "assure" reflects OSHA's position that employers have the authority to impose and enforce reasonable work rules and make compliance with them a condition of employment. As reflected in the testimony of the industrial hygiene witnesses recited above, OSHA's experience has been that if employees understand the need for these provisions and if the hygiene rules are imposed fairly, employers will find their employees will cooperate in complying with these rules. Therefore, comments which objected to the word "assure" as "unrealistic" have been in OSHA's experience considerably overstated.

13. Medical Surveillance (Paragraph n)

(a) A requirement for a medical surveillance program will be included in each proposed standard for potential occupational carcinogens unless the Secretary explains in the proposal why such a program is inappropriate.

Appropriate medical surveillance programs are mandated by the statute. See section 6(b)(7) of the Act. They must be provided without cost to the employee. As discussed more fully elsewhere, the requirement that medical examinations be provided at "no cost to the employee" is one of the few foreclosed regulatory issues.

The rulemaking record provided much support for the general appropriateness of requiring medical surveillance programs for employees exposed to potentially carcinogenic substances. Many reasons were given. Where there is the possibility of early detection of carcinogenic effect, medical surveillance was characterized as essential. (Murray T. 3549, Thorpe T. 4565, Lam T. 4567, 5595). In addition, medical surveillance will provide ongoing data to refine information as to whether a material is a potential carcinogen (Thorpe 4566), making surveillance additionally appropriate for Category II potential carcinogens.

The usefulness of periodic examinations "often" will extend to the employee's general health, independently of any questions of carcinogensis (Lamm. Tr. 4567). In addition, the relationship between host susceptibility and exposure makes all health data relevant to the diagnosis of potential cancer.

(b) The details of the medical surveillance program, however, will be left to the rulemaking record of the substance-specific proceeding. The details include the frequency, protocols of the examinations, the content of the reports required from the examining physician, and the information given physicians by the employers.

Some questions related to the larger issues of access to medical records were raised in the Cancer Policy hearing. Since these issues are the subject of an ongoing rulemaking, and a final standard is expected to be promulgated shortly, OSHA has deleted from the models any provisions concerning access to medical records.

The proposal had set forth OSHA's typical medical surveillance program requirements. In pertinent part, the proposal provisions were as follows:

> The model standards require that the medical surveillance program provide each covered employee with an opportunity for medical examination. As noted above, the authority and requirement for this provision are found in section 6(b)(7) of the Act.
>
> All examinations and procedures are required to be performed by or under the supervision of a licensed physician and provided without cost to the employee. While the physician will usually be selected by the employer, the standard does not so mandate, leaving the employer free to institute alternative procedures such as joint selection with the employee or selection by the employee. Clearly, a licensed physician is the appropriate person to be conducting a medical examination. However, certain parts of the required examination (e.g., taking a history) do not necessarily require a physicians's expertise and may be conducted by another person under the supervision of the physician. As noted above, the Congress has mandated, by reason of section 6(b)(7) of the Act, that medical examinations and procedures required by OSHA standards be provided at no cost to the employee.
>
> The model standards provide that a work history, medical history and medical examination be performed. The purpose of this requirement is to establish a baseline health condition against which changes in an employee's health may be compared in the detection of changes in physical condition.
>
> The model standards leave blank the specific medical protocols for the examination. The various tests that comprise the medical examination to be prescribed in the individual rulemaking are determined by the specific toxicology and effects of each substance. The tests that are designed to be used in an initial assessment of an employee's health and to detect changes in health which may occur are to be required as appropriate. Of course, if additional tests and procedures are appropriate for a given substance, they may be added in the specific rulemaking covering that substance.
>
> The model standards require that the employer provide the physician with certain specified information. This information includes a copy of the regulation, a description of the affected employee's duties as they relate to the employee's exposure, the results of the employee's exposure measurement, if any personal protective equipment is used or is to be used, and information from previous medical examinations of the affected employee to the extent that they are not readily available to the physician. The purpose in making this information available to the physician is to aid in the evaluation of the employee's fitness to wear personal protective equipment when required. It should be noted that the model standards do not require that a copy of the regulation be given to the physician for each

employee. One copy would be sufficient, provided that the employer assures that the physician is aware of which employees are covered by this standard. Items that relate to individual employees or categories of employees (such as the description of job duties) need be transmitted to the physician only once, unless, for example, the duties change. Exposure measurements will be cumulative, so that the results of each monitoring are to be sent to the physician. However, since sampling will be done on a representative basis, the language of the model standards requires the physician to be given either the employee's actual exposure measurements, if available, or the estimated level of the employee's exposure based on the relevant representative measurements.

The employer is required to obtain a written opinion from the examining physician containing: the physician's opinion as to whether the employee has any detected medical conditions which would place the employee at increased risk of material impairment of health from exposure to the toxic substance; the results of the medical tests performed; any recommended limitations upon the employee's exposure to the toxic substance and upon the use of protective clothing and equipment such as respirators; and a statement that the employee has been orally informed by the physician of any medical conditions which require further examination or treatment. This written opinion must be relevant to specific findings or diagnoses unrelated to occupational exposure, and a copy of the opinion must be provided to the affected employee. The purpose in requiring the examining physician to supply the employer with a written opinion containing the above mentioned analyses is to provide the employer with a medical basis to aid in his determination of the employee's initial placement and continuing capability to use protective clothing and equipment. Requiring that the opinion be in written form will serve as an objective check that employers have actually had the benefit of the information in making these determinations. Likewise, the requirement that the employee be provided with a copy of the physician's written opinion will assure that the employee is informed of the results of the medical examination and may take any appropriate action. The purpose in requiring that specific findings or diagnoses unrelated to occupational exposure not be included in the written opinion is to encourage employees to submit to a medical examination by removing the fear that employers may find out information about their physical condition that has no relation to occupational exposures.

During this rulemaking, participants raised the question of adverse health risk to workers because of the performance of required medical tests and procedures. (e.g., Lamm. 4567). In particular, mandating frequent x-rays was cited (e.g., 4568) as creating its own risk of cancer (see, e.g., #143).

In response to this concern, OSHA has deleted the provision in the guidelines that the initial physical examination be conducted with any specific protocol.

OSHA intends that the question of the appropriateness of diagnostic x-rays, as well as other procedures, should be considered in subsequent proceedings and should include the question of the risk, if known, of the procedure itself.

The model medical surveillance provision applies to each employee who is or will be exposed to the substance. (§ 1990.160(n)(1)(i). Some participants questioned the breadth of this requirement. In some standards regulating carcinogens, OSHA has limited the required administration of medical tests and procedures presenting their own risk of adverse health effects to "high risk populations" (See, e.g., the discussion in the preamble to the coke oven emission standard, 41 FR 46777–46779). The problems in defining a "high risk population" were also discussed in the coke oven emission preamble.

The question of defining a high risk group, like determining other cut off points for various aspects of medical surveillance programs and determining frequencies of various protocols, cannot be decided in the abstract. "High risk" was defined in relation to exposure levels and to frequency and duration of exposure for purposes of mandating sputum and urinary cytology. (41 FR 46779). Similarly specific tests may lead to cut-offs in future standards.

Thus, appropriate cut-offs, if any, for prescribing any medical surveillance for any exposed employees must necessarily be shaped in a single substance rulemaking. OSHA also will use the action level concept, where appropriate, as well as the coke oven emission approach, i.e., identifying employees with longer term exposures, for certain tests. In some cases, all exposed employees may be covered by the medical surveillance requirements.

Another issue discussed at the cancer policy proceedings was whether, as proposed, employer-supplied medical examinations may be administered solely by employer-retained physicians. Most union participants strongly argued against allowing examinations by "company doctors" to satisfy the standard. (See, e.g., Tr. 5842, 5843, 5933, 5934). Solutions urged by union participants and others were to give the employee the right to choose his own examining physician (Tr. 5916); and to obtain a second medical opinion from a physician of the employee's choice (Tr. 5933 ACTUU).

Industry participants supported the proposal's provisions for employer-selected examining physicians. For example, API argued that convenience and efficiency would be fostered by employer-selected physicians. API pointed out that its member companies often use outside occupational health specialists as well as in-house personnel. (API comments on model standards). It was suggested that unless examinations are performed by "adequately trained occupational physicians, they will largely be a waste of time," and that in-house or outside occupational health specialists are in a far better position than individual private practitioners to identify group trends and risks and report them to employers without infringing on workers' privacy rights (API, Ibid., 54–44).

OSHA agrees with the United Auto Workers representative who stated he doubted "whether it is possible to modify the entire company-doctor system in the context of this hearing on the cancer policy" (Tr. 5843). Therefore, OSHA has retained the proposal's requirement that the employer provide affected employees with opportunities for medical examinations and procedures performed under the supervision of a licensed physician, and which shall be provided without cost to the employee. This requirement would not preclude the institution of the suggested alternatives, such as employee-designated physicians, but would not require such designation.

Another alternative suggested was a multiple physician review procedure. However, very little evidence was introduced to support the need for such a provision as part of the Cancer Policy.

14. Employee Information and Training (Paragraph o)

There will be a provision for employee information and training unless the Secretary explains why such a provision is inappropriate. As recited in the preamble to the proposal:

> The three model standards uniformly require the employers to provide a training program for employees exposed to the toxic substance. OSHA believes that an information and training program is essential for the protection of employees because an employee can do much to protect himself if he is informed of the nature of the hazards in his workplace. To be effective, an employee education system must, at a minimum, apprise the employee of the specific hazards associated with his work environment. For this reason, the employer would be required to inform each employee exposed to the toxic substance of the nature of the toxic substance-related health problems, and the necessity for exposure control and medical and industrial hygience monitoring programs.
>
> The three model standards also require that the training program be provided at least annually. The content of the training program is intended to apprise the employees of: (1) the hazards to which they are exposed; (2)

the necessary steps to protect themselves, including avoiding unnecessary exposures, respiratory protection and medical surveillance; (3) their role in reducing exposures to the toxic substance and (4) their rights under the standard. Section 6(b)(7) of the Act makes it clear that these are appropriate goals of an employee training program, and the model standards, therefore, include them.

The employer is required to make a copy of the model ETS and proposed and final standards, as applicable, as well as the appendices, available to the affected employees. This requirement, in combination with the review provided for as part of the training program, is intended to assure that employees understand hazards and the requirements of the applicable standard.

More so than with any other proposed provision of the models, the education and training requirements were supported by the entire spectrum of participants in the cancer policy rulemaking.

Examples of industry support include Dr. Jawschke of Stauffer, who testified that it was "absolutely essential that the worker receive information on . . . things he is exposed to and which may present a risk to him" (Tr. 6700). Similarly, Dr. Casey of General Electric agreed that it is appropriate to train employees about hazards of working with potentially carcinogenic materials" (Tr. 7903).

Dr. Lange of Dow, who recommended that the training provisions be "guidelines" rather than compulsory standards, agreed that the required components of training programs in the proposed models are "in general, the type of things which should be included" (Tr. 5203).

Union testimony approved the requiring of comprehensive training programs at minimum frequencies. The need for such training was dramatically shown by some hearing testimonies. Some employees testified they got no training and were ignorant of chemical and physical hazards in their plants, including carcinogenic hazards (Tr. 6997, 6106, 6111, 6147, 6187). Other employees testified they "are at their (employer's) mercy" in receiving information that something may be carcinogenic and receive only selective information (Tr. 6221). Union officials testified that plants handling substances regulated by OSHA tended to have better training programs than other plants where potential carcinogens were not regulated (Tr. 5770, 5771).

Industry representatives agreed that the value of training and education spills over to the entire industrial hygiene program. Employees can appreciate the utility of requirements (Tr. 5942, 6700), and thus are motivated to participate in the implementation of other provisions.

One point of contention was the scope of the training requirements. API criticized applying the provision to "all employees where there is occupational exposure to a substance," stating this created "unnecessary coverage" (Exh. 252, B, 59). They cited the inorganic arsenic standard as showing the suitability in some circumstances of restricting coverage to employees exposed above the action level, or for whom there is a risk of exposure-related eye or skin irritation. Since the details of the training provisions will be determined on a case-by-case basis, the cut-off point for training will be an issue in the proceeding.

15. Signs and Labels (Paragraph p)

(a) There will be a provision for signs and labels which warns employees of the cancer hazard for Category I potential carcinogens unless the Secretary explains why such a provision is inappropriate.

The preamble to the proposal had set forth the reasons for this provision as follows:

OSHA believes that it is important and indeed section 6(b)(7) of the Act requires, that appropriate forms of warning, as necessary, be used to apprise employees of the hazards to which they are exposed in the course of their employment. OSHA believes, as a matter of policy, that employees should be given the opportunity to make informed decisions as to whether to work at a job under the particular working conditions extant. Furthermore, OSHA believes that when the control of potential safety and health problems involves the cooperation of employees, the success of such a program is highly dependent upon the employee's understanding of the hazards attendant to that job.

In light of the serious nature of the hazard of exposure to carcinogens, OSHA does not believe that periodic training alone will adequately apprise employees of the carcinogenic hazard. However, coupled with the training requirements, OSHA believes that the requirement to post signs will adequately do so. Additionally, the appearance of the phrase "cancer hazard" or "potential cancer hazard" on the warning sign will assure that employees are actually being informed of this hazard.

Since even persons who are exposed to a carcinogen only occasionally may face an increased risk of cancer, OSHA does not believe that the hazard to these people is overstated by the required signs. Also, as is the case with a regular employee, the warning signs would serve as an added impetus to occasionally visiting employees to utilize any protective equipment which has been provided.

Finally, given the evidence of the carcinogenicity of substances, OSHA believes that signs will not cause undue alarm. This is especially so when balanced against the positive results anticipated, as described above. For all of the reasons set forth, OSHA believes that it is appropriate to use precautionary signs which warn of a cancer hazard. Additionally, the phrase "authorized personnel only" relates directly to requirements in the Category I permanent standard which limit access and activities within regulated areas.

The words "danger" or "caution" are used for three reasons: (1) To attract the attention of workers; (2) to alert workers to the fact that they are in a dangerous area, i.e., an area where they are exposed to a potential carcinogen; and (3) to emphasize the importance of the message to follow.

The use of labels or signs required by other statutes, regulations, or ordinances in addition to, or in combination with, signs required by this standard is permitted. OSHA recognized that employers may be subject to various legal requirements to use warning signs and labels. The purpose of this provision of the standard is to allow the employer to comply with these various requirements in an administratively convenient manner.

The standard requires that no statement which contradicts or detracts from the effect of any sign required by this paragraph shall appear on or near any such required sign. They also require that the legend on the signs be kept visible to employees by illuminating and cleaning the signs when necessary. These two requirements are designed to ensure the effectiveness of the warning signs.

Statements which contradict or detract from the intended effect of the sign are clearly counterproductive to using signs to convey information. Similarly, if the legend on the sign cannot be read because of either darkness or an unclean condition, then there is no purpose in requiring signs to be posted.

The use of precautionary labels on containers of protective clothing contaminated with the toxic substance is required. We are mindful that no evidence may presently exist that laundry workers who handle contaminated clothing containing any specific carcinogen exhibit an excess of cancer. However, no evidence exists to the contrary, and in light of our experience with other carcinogens (e.g. asbestos) and the preventative nature of the Act, we have decided to include a requirement for precautionary labels for contaminated clothing. Moreover, OSHA believes it is as appropriate that individuals who are engaged in handling and laundering the contaminated clothing be apprised of the hazard and practices to be avoided when handling the clothing as it is to inform the other primary employees.

OSHA believes the fundamental reasons stated in the preamble to the proposal are supported by this rulemaking record.

These reasons for sign posting were amplified during the hearing. Employees who worked around signs indicating that vinyl chloride was a "cancer-suspect agent" testified they find sign posting very helpful. It reminds them of what atmosphere they are in, they can act accordingly and they know what

obligation the company is under in handling this product (Tr. 5902). Opposition to these requirements, which was expressed during the rulemaking hearing, did not contest the reasons for requiring signs and labels, but objected to the wording as stress-inducing (e.g., PMA #116); the number of signs as excessive (#163) (e.g. #218 AISI) and the requirements that labels be affixed on containers leaving the workplace as exceeding OSHA's jurisdiction. It was also suggested that large numbers of signs will reduce their impact (e.g. #218 AISI, #163 Upjohn).

The main opposition to OSHA's requirements for posting signs using the word "cancer" was provided by the Polyurethane Manufacturers Association (PMA) (see #116, Tr. 7042 et seq.). The crux of PMA's complaint is that OSHA's proposed wording for signs would be a "scare factor" (T. 7051). PMA presented an expert on the "human factors" design of signs, labels and instructions who testified that the signs and labels proposed by OSHA "are a failure in almost every respect", (Dr. Chapanis, Tr. 7072 et seq.). The "most serious failure" according to Dr. Chapanis, is that neither OSHA or NIOSH conducted any genuine tests, experiments or surveys on the proposed signs or labels, and therefore they violate existing standards for the preparation of warning signs (Tr. 7072–7073). However, we note that the "standards" and examples discussed by Dr. Chapanis relate to "accident prevention" (Tr. 7073, 7074) and to a standardized sign system that was developed without regard for chronic, long term biological risks such as cancer.

Dr. Chapanis' empirical evidence on the utility of OSHA's proposed signs to allow workers to arrive at informed decisions were "some small tests, not really good tests," which he conducted (Tr. 7073).

Also, although Dr. Chapanis and other witnesses provided by PMA said that using the word "cancer" would cause emotional stress, other witnesses objected to the signs and labels required on the ground that the number of signs required would cause the warnings to be ignored.

API, PMA and other industry groups have suggested that rather than bearing the legend "cancer hazard" or "potential cancer hazard", labels indicate the "nature or strength of the underlying evidence of carcinogenicity" (B, 62). OSHA disagrees. We believe the proposed designations of "cancer hazard" and "potential cancer hazard" reflect the underlying evidence. Including such information as the number of animal tests on a label as suggested by Dr. Chapanis would clutter the limited space of the label.

The proposal explained the labeling requirement and the reasons for their prescription as follows:

> As to labels, due to the hazardous nature of exposure to a potential carcinogen, OSHA believes that emphasis should be placed on warning employees and other persons about the danger of exposure. For this reason, the model standards include a requirement that caution labels be affixed to all containers containing the Category I and Category II toxic substance and of the products containing it, not only because of the hazardous nature of this exposure, but because of the related necessity for both the employer and employee to know whether the product contains any of the carcinogen. The labeling provisions for the model standards for the Category I and Category II toxic substance also require the employer to assure that caution labels are affixed to any product containing the toxic substance when such product leaves the employer's workplace. This proposed requirement is designed to protect any other employees who will be handling, transporting, or using this product. Thus manufacturers and suppliers would be required to affix caution labels. The rationale for this requirement is that the manufacturer or supplier is in the best position to know whether the product does contain the Category I and Category II toxic substance and should therefore be required to inform employees of even other employers of the hazards to which they are being exposed.

Testimony indicated that often labeling as to contents of containers was the only source of information about its content, which in turn was essential to assessing the potential for exposure of employees or appropriate handling procedures (T. 7177–7178).

Some industry representatives testified it was their company's practice to generically label their products when they leave the plant (e.g. T. 6643, Union Carbide), and to label their tanks inside the plant with the generic chemicals they contain (T. 7944). OSHA believes, therefore, that the general requirement to label containers constitute responsible industry practice and, unless shown inappropriate in a particular standard setting proceeding, should be included in the standard.

The details of the signs and labeling provisions will be resolved on a case-by-case basis. Thus, for example, the triggering point for the provision would be an appropriate issue for the individual proceedings.

Whether a signs and labels provision will be included for Category II potential occupational carcinogens will be determined on a case-by-case basis.

As noted elsewhere, the Secretary has retained wise latitude in the regulation of Category II carcinogens. Since regulation of such a substance may, in some circumstances, be based substantially upon other toxic effects, it may be inappropriate to have a signs and labels provision that warns of the cancer hazard. On the other hand, there may be circumstances where such a provision is appropriate. Therefore, the determination will be made on a case-by-case basis.

16. Recordkeeping (Paragraph q)

There will be a recordkeeping provision unless the Secretary explains why such a provision is inappropriate.

The proposed model standards had discussed the detailed provisions and reasons for requiring that records be maintained of exposure monitoring and medical surveillance. The detailed provisions of recordkeeping will be determined on a case-by-case basis. In addition, OSHA is not resolving in the Cancer Policy the issues covered by OSHA's soon-to-be published final standard on Access to Employee Exposure and Medical Records, proposed at 43 FR 3137 (July 21, 1978).

Section 8(c)(3) of the Act mandates the promulgation of regulations requiring employers to maintain accurate records of employee exposure to potentially toxic substances or harmful physical agents which are required to be monitored or measured. Accordingly, such a provision is incorporated in the model standards.

The model standards provide that records should be kept which include information which is intended to identify the employee and to accurately reflect the employee's exposure. Specifically, it should include: (a) the names, social security numbers and job classification of each employee covered by the monitoring; (b) the dates, number, duration and results of each of the samples taken, including a description of the representative sampling procedure used to determine employee exposure where applicable; (c) the type of respiratory protective devices worn by the employee, if any; (d) the environmental variables that could affect the measurement of employee exposure; and (e) a description of the sampling and analytical methods used, and evidence of their accuracy.

The model standards also indicate that the employer should keep an accurate medical record for each employee who is subject to surveillance. Section 8(c)(1) of the Act authorizes the promulgation of regulations requiring an employer to keep such records as are necessary or appropriate for the enforcement of the Act or for developing information regarding the causes and prevention of occupational illnesses.

OSHA believes that medical records (like exposure monitoring records) are generally both necessary and appropriate to both the enforcement of the standards and the development of information regarding the causes and prevention of illness related to exposure to potential occupational carcinogens.

Like all records, medical records serve as an objective check that an employer has actually performed the substantive requirements of the standard. As explained above, these records relate an employee's medical effects with his exposure in order to develop information regarding cause and prevention.

The model standards provide that the medical records should include information which is intended to identify the employee, to accurately reflect the employee's health, and to establish that the employee has had an opportunity to participate in a medical examination. It is also required by OSHA's proposal that the "medical surveillance" file for "each employee" include a copy of the information provided to the physician and a copy of the employee's work history. OSHA agrees that in some cases the items required to be provided to the examining physician, *i.e.*, the personal protective equipment used, the employee's exposure level, and the employee's duties, will have been retained by the employer, either as part of the exposure monitoring record required to be kept by the model standards, or otherwise as part of the employer's routine recordkeeping for other administrative purposes. OSHA, therefore, has adopted API's suggestion that information supplied by the employer to the physician not be required to be kept specifically in the medical surveillance file, by adding an exception to the paragraph (q)(2)(ii) retention requirement as a "medical surveillance record, denominated '(c)', if it is kept elsewhere by the employer for the period of time specified in paragraph (q)(2)(iii)".

API also observed that OSHA is engaged in an ongoing rulemaking proceeding on "Access to Employee Exposure Medical Records" which addresses the questions of providing access to these records by NIOSH, OSHA, employees and their representatives. OSHA intends to apply the access provisions which will be established in that proceeding to all health standards. However, until those regulations are promulgated, OSHA will continue to regulate access on a case by case basis, and the model standards preserve that intention.

17. Observation of Monitoring (Paragraph r)

Each standard regulating exposure to Category I and II substances, including an ETS, will include a general requirement for observation of monitoring by employees or their representatives.

The reason for always requiring such a provision is the requirement in section 8(c) of the Act that employers provide employees or their representative with the opportunity to observe monitoring of employee exposures to toxic substances or harmful physical agents. In accordance with this section, all three model standards contain identical provisions for such observation. To assure that the right to observe is meaningful, observers would be entitled to receive an explanation of the measurement procedure, to observe all steps related to the measurement procedure and to record the results obtained.

Under the guideline the observer, whether an employee or designated representative, should be provided with, and is required to use, any personal protective devices required to be worn by employees working in the area that is being monitored, and should comply with all other applicable safety and health procedures.

In particular with potential occupational carcinogens, OSHA believes an observation of monitoring program can improve the efficiency of the monitoring process itself. This may be so because permissible exposure limits in many cases will be set at low levels and new detection devices may be introduced. OSHA believes that by having employees and their representatives observe monitoring, their cooperation will help in assuring the reliability of monitoring programs, and help to identify, where possible, representative employee exposures. Employees will also be increasingly aware of work situations where exposures are highest and of their work habits which can influence exposures.

18. Provisions for ETS's

Many provisions of the ETS model standard are the same as those for permanent standards. Thus, the lowest feasible level requirement and the requirement that employers provide mandated personal protective equipment and medical examinations at no cost to the employee are the same for both permanent standards and ETSs. The role of scope and application, definitions, PEL, notification of use exposure monitoring and measurement, protective equipment and clothing, housekeeping, respirators, medical surveillance, employee information and training, signs and labels and recordkeeping is the same for ETSs and permanent standards. That is, the program will be required unless the Secretary explains why such a program is inappropriate and the specific details will be decided on a case-by-case basis. While some of the detailed provisions may vary, they are not discussed in depth herein because such provisions are merely guidelines and the differences can be generally ascribed to the short-term and interim nature of ETSs.

The methods of compliance provision for ETSs differ substantially from the permanent standard.

(b) The Model ETS. OSHA has indicated that the provisions of the model ETS are intended to require only those things which are possible to be achieved immediately or within a very short period of time. The model ETS therefore states that OSHA prefers the reduction of employee exposure by way of engineering and work practice controls.

Examples of engineering controls and housekeeping procedures which can be installed in a short time were submitted into the record by Dr. Billings, as follows:

"Short-term controls include housekeeping to reduce access of the material to the workplace (fugitive emissions), work practices which limit time of exposure or which limit the amount of material disseminated or dispersed in the workplace (wet methods of dust control or high efficiency vacuum cleaners, covered containers of liquid or powder, etc.), and temporary local exhaust systems, or some types of general ventilation (e.g., a window exhaust fan). Temporary local exhaust systems of the self-contained type are readily available as complete packages for air exhaust volumes of about 100 cfm up to a few thousand cfm. These may be connected in the process or operations ventilated with flexible exhaust ducts and appropriate hooding, and the exhaust recirculated or directed out of the plant roof. Larger volumes (centralized systems) require larger components, longer times, more resources, and imply regulatory approvals associated with large sources. . . . In my opinion, the use of respiratory protective devices as a means of control of hazards caused by exposure to toxic chemicals in the workplace environment should be limited to the absolute minimum time because they have many disadvantages in use and do not provide positive protection for the workers. If respiratory protective devices are required and must be used for a temporary period, then the use of self-powered air purifying types should be encouraged (contain pump, motor, battery, air purifying component such as a filter, absorbent as appropriate to the toxic constituent in the environment, and a hose to

a positive pressurized oro-nasal or face mask pressurized face shield)." (Billings, St. 12–13).

It also recognizes, as a practical matter, that in some instances the immediate reduction of exposure will be primarily through the use of respiratory protection and the institution of good housekeeping practices and other work practices. The model ETS recites recommended work practices which may be easily instituted to help reduce exposure. They should be implemented even where they do not fully reduce exposures to or below the PEL. The methods of compliance, therefore, are a major difference between the model ETS and the model 6(b) standards. One other major and distinctive feature of the model ETS is the requirement that during the effective period of the ETS (6 months) employers must look down the road to the model permanent standard for the Category I Potential Carcinogen and start planning how to reduce exposures to the lowest feasible levels solely by way of engineering and work practice controls. Thus, OSHA anticipates that by such requirements delayed effective dates of the permanent standard can be limited or perhaps avoided altogether, hastening the reduction of employee exposure to the toxic substance. Because of the general irreversibility of cancer as pointed out above, OSHA considers the early reduction of employee exposures the most significant provision in decreasing the risk of cancer.

The Record in this proceeding supports the proposal (see e.g. duPont) and OSHA therefore has adopted the proposed methods of compliance provision.

The model ETS does not include requirement for the designation of regulated areas. As has been explained, the ETS requirements are those that OSHA has determined and believes can generally be instituted immediately or fairly quickly. Yet, before a regulated area is required, employers would be required to monitor to determine which, if any, employees are exposed to the toxic substance over the permissible exposure limits. OSHA believes that with the present requirements of the model ETS, it would not be feasible in many cases to add this additional requirement to the model ETS. Similarly, it would normally not be possible to design and build hygiene facilities within the life of the ETS. Accordingly, hygiene facilities will generally not be required in ETS standards.

XI. ECONOMIC AND ENVIRONMENTAL CONSIDERATIONS

A. ECONOMIC CONSIDERATIONS—GENERAL

1. The Proposal and Introduction

The proposal provided that one of the issues to be considered in a rulemaking concerning a Category I Toxic Substance was "the determination of the lowest feasible occupational exposure." OSHA intended that the inquiry under this issue include relevant technological and economic considerations. The final regulation makes this intention explicit by inserting the words "including technological and economic considerations" in § 1990.146(i).

Mr. Wrenn, OSHA Director of Health Standards, expanded on the proposal's discussion of feasibility in his opening statement for the agency and in answers to questions on the first day of the cancer policy hearing. He pointed out that feasibility included technical and economic considerations as a whole (Wrenn, Tr. 34) and that the term was best defined in the context of the statute, court decisions and prior OSHA regulations such as arsenic, coke oven emissions and others where the concept was applied to a concrete factual record (Wrenn, Tr. 115, 159). He stated that OSHA would continue under the cancer policy to perform economic and technical assessments similar to those done in the past (Wrenn, Tr. 62). Mr. Wrenn pointed out that since the cancer policy did not regulate any specific substance, it was more appropriate to conduct studies of economic consequences in the regulation of specific carcinogens (Wrenn, Tr. 174, S. 6).

Because technological and economic considerations are factors in determining the lowest feasible level, the proposal pointed out that an economic assessment would be performed pursuant to relevant Executive Orders in individual rulemakings where appropriate (42 FR 54128). The concept of feasibility in the Act, as interpreted in the leading case *I.U.D. v. Hodgson*, 499 F. 2d 467 (D.C. Cir. 1974) makes it clear that certain economic considerations are included within that term, and that therefore they are issues in individual 6(b) rulemakings. Since these considerations are issues for the individual rulemakings pursuant to the OSHA Cancer Policy, it is not necessary that they be resolved in this policy rulemaking.

These proceedings produced extensive public comments on the appropriate role that economics should play in this rulemaking itself and in the regulation of carcinogens in individual rulemakings that might be taken pursuant to this general policy. There is a substantial amount of evidence in the Record concerning economic considerations. This consists of the OSHA Regulatory Analysis, oral testimony from the extensive public hearings, numerous written comments, exhibits submitted by interested parties in response to the proposal and a cost impact study (the Snell report) performed for the American Industrial Health Council (AIHC).

While the expressed economic concerns often dealt with specific provisions of the proposal, analysis of the Record indicates that the economic considerations can be generally divided into issues relevant to the overall policy objective of reducing the incidence of occupationally related cancer and those dealing with the preferential method for reaching this objective. The next section (Section 2, *Summary of the Record*) summarizes the major economic testimony but does not draw any conclusions. Section 3 (*Summary of OSHA's Conclusions*) briefly summarizes the relevant economic issues and OSHA's conclusions. Finally, Section B (*Discussion of the Economic Factors in Specific Issues*) is divided into nine parts that discuss specific economic considerations. It analyzes in detail the economic evidence and explains OSHA's conclusions. That section focuses primarily on the economic aspects of those issues and provides cross references to the discussions of the non-economic aspects of these issues in other parts of the preamble.

2. Summary of the Record

The Record indicates general agreement that one of the major reasons why it is necessary to regulate occupational carcinogens is because of their "externality-generating" nature. Externalities result in an inefficient allocation of the National resources because market prices fail to reflect the social costs of production. The resulting distortions in relative prices lead to the excess consumption of commodities produced in high-risk industries. See, for example, the testimony of Drs. Ashford (MIT) (Ashford, Tr. 2489–90) and Lave (Carnegie-Mellon) (Ex. 117, pp. 10–11). Disagreement among some witnesses centered on the degree of health protection necessary to insure optimal internalization of occupational disease costs.

The AIHC presented Dr. Richard Wilson, a physicist from Harvard University, who recommended a specific procedure (comparative risk or risk-

benefit analysis) for defining health protection in terms of acceptable risk levels (Wilson, S. III–104D). Dr. Wilson performed calculations of single point-estimates of risks which humans voluntarily accept (e.g., engaging in certain sports activities) or involuntarily live with (e.g., being a pedestrian in a motor age). He also derived single-point estimates of excess risk for specific carcinogens. Section VIII on risk assessment discusses whether single-point or range estimation is more appropriate. The estimates of voluntary and non-voluntary risks were to provide benchmarks in his view to OSHA in regulating occupational carcinogens.

Dr. Wilson employed these point-estimates of "acceptable risk levels" to develop the boundaries for a detailed regulatory framework. For occupational risks higher than those which he argued individuals voluntarily accept, defined as one death per 100 exposed workers per year, risk would be reduced irrespective of the costs, including a ban on the hazardous activity if necessary. In contrast, no regulatory action would be undertaken for risks less than 1 death per 100,000 workers annually. In Dr. Wilson's view, intermediate risks for chemical carcinogens would require control measures only to the extent that the margin abatement costs per life saved did not exceed one million dollars.

The Record contains extensive comments on the difficulties involved in performing quantitative risk assessments, especially of carcinogens. As discussed in Section VIII, many participants to this rulemaking pointed out that such estimates are crude and highly uncertain and may actually underestimate risks by many orders of magnitude. The AFL–CIO and the United Steel Workers of America (Ex. 261), for example, reviewed the scientific bases for risk assessment at great length and concluded that the available scientific methodology permits only highly speculative risk assessments. They argued that risk assessments of carcinogens are likely to err systematically downward (underestimate human risk) because of the much greater genetic variability in humans than that which exists in test animal species and because employees, unlike clinical test animals, are exposed to a great number of toxic and possibly carcinogenic substances likely to induce synergistic effects. They concluded that, "the record indicates that the potential for misleading impressions of safety from risk assessments are great." (AFL–CIO, P.H. Brief, Ex. 261 pp. 81–82).

In response to Dr. Wilson's testimony, Dr. Ian C. T. Nisbet, an OSHA consultant, filed a comment directed to Dr. Wilson's estimates of occupational risks (Ex. 224–E). Dr. Nisbet re-calculated Dr. Wilson's risk assessments for industrial carcinogens and concluded that point-estimates of risks in excess of 9 to 40 times Dr. Wilson's projections could be defended. Dr. Wilson responded (Ex. 251b) that in 2 cases, his estimates were better than Dr. Nisbet's and that in one case his estimates were based on different assumptions.

Other parties discussed the concepts behind Dr. Wilson's methodology for determining "acceptable" risk based on historically observed levels of voluntary or involuntary risks. Dr. Lave (Ex. 117) discussed at length various research attempts to analyze the risks that humans are willing to accept. He discussed the conceptual and practical difficulties inherent in evaluations of risk, including the large variations in the risks that humans view as acceptable, the difficulties that individuals face in assessing risks, and the characteristics of risk that influence individual preferences for risk. These dimensions include whether the risk is voluntary or imposed, familiar or unknown, controllable or uncontrollable, of immediate occurrence or indeterminate in the future, and whether the risk affects large numbers of humans with low probability or small numbers of individuals with high probability (pp. 17–19). He also stated,

> "Another major complication evolves from intertemporal changes in preferences due to higher standards of living and improved knowledge. The higher our standard of living, the more protection and greater safety we desire (are willing to pay for); also, the greater our knowledge about the adverse effects of exposures, the more we desire to lower exposures." (pp. 23–24).

The AFL–CIO and United Steel Workers of America argued (Ex. 261, pp. 70–87) that regulation of potential occupational carcinogens cannot be based on a comparison between risks voluntarily accepted and the involuntarily and largely unknown risks which workers face. They stated:

> "While ivory tower theorists and model builders testified that this was not so (according to industry witnesses risk faced by workers are voluntary and known—See Wilson, Lamn tr. 4525, Lave), the testimony of many workers show that knowledge and choice are not luxuries shared by all" (AFL–CIO, Tr. 6124, 6170).

Dr. Ashford (MIT) stated that this Nation clearly preferred actions which would prevent major disasters, even if it would mean that in some areas regulations would in retrospect be stricter than absolutely necessary (Ashford, Tr. 2492–4). (He called this concept the "minimization of regret.") Health hazards are regulated in a state of imperfect knowledge. Society prefers strict regulation which would catch and prevent the thousands of excess deaths caused by potential carcinogenic substances such as asbestos which in retrospect was much more hazardous than originally envisioned.

Some parties recommended the use of formal cost-benefit analysis as the decision rule for achieving efficient levels of control. (See, for example, Dr. Wilson's approach to the control of intermediate occupational risk levels discussed above). Under this framework, social costs and benefits would be expressed in terms of their monetary equivalents, summed and then compared. Carcinogens would be regulated only to the extent that the benefits of improved health (including longevity) exceeded the costs of hazard abatement.

Other parties recognized the complexities inherent in defining the overall boundaries of occupational risk levels that society is willing to accept and therefore focused their proposals on regulatory methodologies which they believed would more efficiently allocate the Nation's total health resources however defined. They recommended that cost-benefit or cost-effectiveness analysis form the primary basis for determining priorities for regulation and for setting standards controlling individual carcinogenic substances.

API presented testimony of two economists, Dr. Richard Zeckhauser (Harvard University, S. III–125, pp. 717 et seq.) and Dr. Lave (Ex. 117). They recognized the philosophical and practical difficulties inherent in reducing the benefits of improved health to a monetary dimension, particularly where the valuation of human life was involved. Dr. Lave, for example, stated that the notion of explicitly placing a dollar value on life (or, alternatively stated, placing a value on premature death or morbidity) "repugnant" but stated that failing to attempt to make such valuations would be "capricious behavior." (p. 13).

Both Drs. Zeckhauser and Lave argued that placing a monetary value on human life is not necessary to achieve optimal allocation of available health resources. They recommended a cost-effective approach both to structure priorities for regulatory actions and to set standards.

It should be noted that the term "cost-effective" has two meanings. It refers to a mathematical form of analysis described below. It is also used as an

adjective describing the least-costly method of achieving a particular level of health benefits.

The cost-effectiveness analysis advocated by Drs. Lave and Zeckhauser would involve estimating risks to workers and compliance costs at alternative levels of exposure for each substance. The cost and risk reduction estimates at various exposure levels for substances would be integrated into a framework for regulation. Industrial substances would be ordered and regulated to levels according to the number of lives saved per dollar expended. They stated that OSHA should first regulate the substance to the level which would save the most lives per dollar of control costs, then the next substance to the level which would save the second greatest number of lives per dollar, etc. They argued that OSHA should continue to regulate until the cost to save one life was greater than the risk that the Nation was willing to accept (however determined).

Under this procedure, exposure levels set might be higher than the lowest feasible level, as defined by OSHA. Whether this would be the case for individual substances would depend on the estimated costs to reach various exposure limits and the estimated number of lives which could be saved by spending equivalent sums in other health and safety activities.

Dr. Zeckhauser would expand his matrix of possible regulatory outcomes to include alternative control strategies, non-carcinogenic health effects, and even non-occupational health actions (highway safety, hospital construction, etc.). While Dr. Zeckhauser did not specify acceptable risk levels, he argued that we, as humans and as a Society, often tolerate substantial levels of risk despite technologies to eliminate them.

AIHC and API submitted lengthy post hearing briefs (Exs. 251 & 257 respectively) which summarized the views of many participants concerning a policy for regulating carcinogens in this hearing. These parties argued that the OSHA Cancer Policy is designed to achieve a "risk-free" Society, and that this is an undesirable goal because it is impossible to achieve and wasteful of economic resources.

They supported a generic approach to the regulation of carcinogens, but suggested a format designed to achieve the most health protection for each dollar of regulatory expenditures. Technological, economic and risk assessments would be performed for each proposal. This information would then be formally integrated into a cost-benefit or cost-effectiveness analysis. While no specific regulatory response was to be required by the cost-benefit analysis, any final regulation would explicitly take into account costs and benefits. Under this approach, the lowest feasible level would not automatically be set for Category I carcinogens; rather costs and benefits would be used as part of the regulatory process to determine the "reasonably necessary" level of risk. Finally, they suggested that a more efficient use of Society's resources would flow from a more flexible approach to the model standards.

The Regulatory Analysis Review Group (RARG, Ex. 253) also proposed economic efficiency criteria. They recommended that OSHA undertake risk analysis of individual substances to be regulated, perform balancing between social costs and benefits, and modify model standards to increase their flexibility and performance orientation.

Other parties to the proceedings criticized this approach. The Natural Resources Defense Council, the Oil, Chemical and Atomic Workers, the Environmental Defense Fund and the Urban Environment Conference argued (Joint P.H. Brief, Ex. 268) that risk assessment and cost-benefit analysis were not appropriate. They stated that the available evidence is so imprecise as to hold little predictive value. Indeed, they would just be "hid(ing) political judgments, numbers and decision-making behind jargon" (p. 44) and would greatly delay needed regulation. They also argued that it was irrelevant to compare health risks which we voluntarily incur to occupational risks which are not voluntary. Finally, they argued that the Act does not permit such cost-benefit judgments to be made (pp. 43–45). They urged that exposure levels be set as low as technically feasible or zero, if necessary, because of the high health risks of carcinogens.

Dr. Nicholas A. Ashford (MIT, Tr. 2396–2411) testified that cost-benefit criteria, while useful as analytical tools, were not appropriate as decision rules for occupational health regulation. He argued that occupational health differed from some environmental problems. The public, by and large, equally benefited from and paid the costs for cleaner water. If a cost-benefit analysis determined that the costs necessary to achieve cleaner water exceeded the benefits, the same public would forego both the reductions in risk and water quality and the regulatory costs. However, in the case of occupational safety and health, different groups enjoy the economic savings of not regulating and take the risks. Consumers save through lower prices and employers benefit through higher profits from not regulating, while risks are borne by workers, often in the lower economic groups. Therefore, occupational safety and health posed an "equity" question. Dr. Ashford believed it was inappropriate to ignore equity considerations and pay attention to efficiency criteria alone. He believed that cost-benefit analyses are not neutral when the costs and benefits accrue to different parties. Therefore, Dr. Ashford stated that efficiency criteria cannot form the major basis for decision-making on occupational health questions and that inequalities in the distribution of costs and benefits must be given heavy consideration.

In Dr. Ashford's view, both the language and legislative history of the Act made it clear that the Congress intended to weigh regulation heavily on the side of worker protection. He testified that those who argue that cost-benefit analysis should be central to health regulation are trying, by making seemingly neutral arguments, to circumvent the decision by the Congress that health regulation should be highly protective of employees.

The AFL–CIO and United Steel Workers of America (P.H. Brief Ex. 261) stated that they supported OSHA's policy to set the level for carcinogens at the lowest level feasible, a concept that includes technical and economic considerations. They argued that this constituted good public policy because there are no safe levels demonstrated for carcinogens and setting the lowest feasible level comported with the major court decisions upholding previous OSHA standards such as *IUD* v. *Hodgson*, 499 F. 2d 478 (D.C. Cir. 1977) and *AISI* v. *OSHA* (3rd Cir. 1978). This policy followed a sequence that included doing a technical and economic study of the effects of the individual standard on the affected industry, then setting the level achievable with generally known engineering controls (or those reasonably likely to be developed or adopted), and then considering the economic impact of that level. They argued that a reasonable interpretation of the Act and its legislative history would indicate that OSHA was not to take economics into account in writing health standards, but to place first emphasis on health considerations, (p. 20 et. seq.). They also pointed out that:

"The assessment of costs and benefits are plagued with many methodological and philosophical problems—validation of cost estimates, measurement of benefits, choice of discount rates, value judgments about the worth of a human life, all of which limit their

predictive value and render them meaningless for setting stardards to protect workers health." (p. 93)

Mr. Joseph Odorcich, Vice President of the United Steel Workers of America, summarized the views of the AFL–CIO concerning the proposal (Tr. 5640–5705). Mr. Odorcich stated that the evidence available for most potential carcinogens is not sufficient to permit assessments of risk with any confidence and that more importantly, there is no evidence that any money saved not reducing exposures to a specific substance to the lowest feasible level would be spent on protecting worker health in other areas.

Mr. Odorcich stated:

"Given the battle over past regulations and the failure of many in industry to adequately protect their workers exposed to recognized hazards, we can only view so called cost-effective regulation as another attempt to legitimize the trade of workers lives for dollars." (Tr. pp. 5700–01)

Several studies attempted to estimate the overall magnitude of the workplace carcinogen problem and hence the total potential benefits or costs associated with the OSHA Cancer Policy. The joint report of NCI, NIEHS and NIOSH estimated the proportion of cancers related to occupational causes and hence, the total potential benefits associated with eliminating exposures to occupational carcinogens (Ex. 224b). The study estimated that at least 20 percent of the U.S. cancer cases annually are related to industrial sources. Other available estimates show both much lower and much higher occupational cancer incidences. (See the extensive discussion in Section III–G.) The Regulatory Analysis Review Group discussed several problems inherent in this study, but agreed that "the study is useful in presenting the order of magnitude of the problem" and hence the potential benefits of the Cancer Policy (Ex. 253).

Several industry participants in this proceeding approached the proposal from the perspective of the overall cost implications of all regulatory action which may be taken in the future pursuant to this policy. The AIHC submitted a report by the Foster D. Snell Division, Booze, Allen and Hamilton (S. III–104 R & S) which attempted to quantify the total costs of certain "scenarios" for regulating carcinogens.

The cost estimates derived from the Snell study were extrapolated from a base of 7 substances and a composite of 8 pesticides. Snell estimated initial start-up costs (capital expenditures) totaling $9 billion to $88 billion with annual costs of $6 to $36 billion depending on assumptions about the number of substances regulated and stringency of control levels.

A number of criticisms were entered in the Record on the Snell Report conclusions and methodology. RARG concluded that "there are a number of major methodological problems with the BAH (Booze, Allen & Hamilton or Snell) study which makes it impossible to place great confidence in its results." (Ex. 253, p. 12). Appendix A of the RARG Report analyzes those problems at length. Nevertheless, the RARG concluded "that the analysis does document the potential for the policy to impose a large drain on the country's resources."

Other parties to the rulemaking rejected the Snell study estimates as even crude indicators of likely cumulative regulatory effects. Both Ruth Ruttenburg (AFL–CIO, Ex. 94) and Dr. Jared E. Hazleton (University of Texas, Ex. 247) presented technical analyses of the Snell Report. They noted a number of major methodological difficulties with the data collection methods, statistical base, extrapolation techniques, and assumptions regarding future regulatory outcomes in the Snell study.

In Ms. Ruttenburg's judgment, the Snell Report underestimated the cost savings from economies of scale (e.g. one set of controls reduces exposures to a number of substances), substitution of safer chemicals, and technological developments. She pointed out that prior studies had commonly overestimated costs and that for the best study available, vinyl chloride, a retrospective analysis indicated not only that the costs were substantially overstated, but that significant technological innovation occurred which was not anticipated in the prospective study.

In Dr. Hazleton's view, the Snell Report took the wrong approach. The proper approach, from a regulatory point of view according to Dr. Hazleton, was to determine the *incremental* cost of OSHA's generic approach to regulating carcinogens versus other possible approaches. He stated that clearly, occupational carcinogens will be regulated in one manner or another and therefore an estimate of the costs of one regulatory approach in comparison to no regulation is inappropriate. Further, Dr. Hazleton pointed out that the study measured only compliance costs and failed to estimate the costs involved in the nonregulation of industrial carcinogens (e.g. premature death, medical costs, government transfer payments, etc).

Dr. Hazelton concluded:

"Given the reliance on confidential data which was not included in the report, and which was elicited in a manner which would tend to bias upward the estimates; the extreme variation in compliance cost estimates among substances for both the substance producing and using industries; the doubtful basis of the selection of the three scenarios; and the frequent reliance on judgments that are not explained, it is not possible to come to any conclusion about the validity of the Snell compliance cost estimates other than that it would be a mistake to place any reliance on them." (p. IV–26–27).

3. Summary of OSHA's Conclusions

OSHA has carefuly considered all the economic issues raised during this rulemaking process along with the available economic and technical evidence. Based on a careful examination of this Record, OSHA has modified certain provisions of the cancer policy where appropriate to assure more flexible and cost-effective regulation.

First, it was suggested that the OSHA proposal did not adequately provide for setting priorities among regulatory candidates and that this would inefficiently utilize economic resources and afford less protection to workers. The final Cancer Policy contains an explicit priority mechanism that better ensures that regulatory efforts are directed at the most serious health problems in the workplace.

Second, it was suggested that the automatic issuance of emergency temporary standards might result in inefficient utilization of scarce administrative and economic resources in the regulation of those substances which are not the most crucial regulatory candidates. The final Cancer Policy has eliminated requirements for the automatic issuance of emergency temporary standards and permanent regulations for Category I Potential Carcinogens. The automatic regulatory response for Category II Potential Carcinogens has also been eliminated. OSHA has determined that the objectives of a generic approach to the regulation of potential occupational carcinogens require a procedure for establishing priorities for regulatory action.

Third, it has been suggested that the proposed model standards were too rigid and that this might waste resources by requiring unneeded provisions. The final OSHA Cancer Policy has increased the flexibility and performance-orientation of the model standards to promote more cost-effective regulation. Model standards will now serve as guidelines for regulatory provisions to be determined in individual rulemakings.

Fourth, the proposal was criticized for not including provisions for action levels and percentage exclusions. It was suggested that in certain circumstances the absence of such provisions might result in very large costs burdens for employers whose employees are exposed at levels substantially below the permissible exposure limit. The final OSHA Cancer Policy includes a provision for establishing action levels and percentage exclusions where appropriate to assure that limited health resources are directed at serious health hazards.

Fifth, it was argued that the suitable substitutes provision in the proposal was too broadly drawn and therefore that it might force substitution where it was not feasible. The final Cancer Policy has modified the suitable substitute provision to explicitly include technical and economic considerations in the determination of feasibility to avoid unnecessary economic disruptions wasteful of society's resources.

Sixth, some parties argued that greater use of respiratory protection rather than engineering controls might reduce costs. The final Cancer Policy, however, maintains the preference for engineering controls and work practices to achieve the required reduction in worker exposure. Substantial evidence in the Record demonstrates that reliance on respirators as a primary control strategy is not as effective as engineering controls because respirators provide less reliability and comprehensiveness of protection. In addition, attempts to justify primary reliance on respiratory protection based on cost-effectiveness are misleading because such analyses fail to include the substantial administrative costs that would be required to make a respirator program as comprehensive as engineering controls and to take into account the greater unreliability of respiratory protection.

Seventh, some parties argued that exposure levels should be set based on cost-benefit criteria. However, the final OSHA Cancer Policy retains the provision that exposures to Category I Potential Carcinogens be reduced to the lowest feasible level taking into account technological and economic considerations. OSHA believes that a cost-benefit approach to setting permissible exposure limits would be inappropriate for three reasons.

First, the state-of-the-art of quantitative risk assessment techniques particularly for carcinogens, that are crucial to cost-benefit analysis, is too crude and unreliable to permit the refined estimates necessary to determine risk reduction at various exposure levels. OSHA believes that estimates with such wide variations that may understate cancer risks by orders of magnitude are not useful in setting control levels. Cancer is an irreversible disease leading to death with no demonstrated threshold or safe level, and thus requires a highly protective regulatory approach.

Secondly, as a matter of policy, efficiency criteria alone are not appropriate because they ignore equity considerations. The economic savings from less protective regulation accrue to industry in the form of higher profits and consumers in the form of lower prices. But the costs are borne by workers through increased industrial illness and death rates. OSHA believes that it would be inappropriate for an agency statutorily required "to assure so far as possible every working man and woman in the Nation safe and healthful working conditions" to ignore such equity considerations.

Finally, OSHA believes that the correct interpretation of the Act requires the agency to reduce worker exposure to carcinogens to the lowest feasible level since no safe level can be shown.

Eighth, the final OSHA Cancer Policy does not freeze science. It provides procedures for individual petitions and periodic agency review (at least every three years) for amending provisions of the Cancer Policy. This insures that technological breakthroughs in respirators or scientific advances in risk assessment techniques can be accommodated to the extent appropriate within the Cancer Policy itself.

Ninth, the Snell study was initially presented as a hard estimate of the costs of the Cancer Policy. It was later argued that though not very accurate, the magnitude of the costs estimated nevertheless indicated that a more elaborate cost study should be conducted by OSHA. OSHA has determined that serious methodological flaws preclude meaningful interpretation of the Snell study results. OSHA believes that the total cost impact of future standards issued pursuant to OSHA's Cancer Policy cannot be reasonably estimated at this time because of the uncertainties surrounding the identity of specific chemical substances to be regulated, exposure levels and other control devices to be established in standards issued for those substances, and the timing of regulations (hence, the identification of appropriate baselines) in ensuing rulemaking procedures. OSHA has also determined that the final Cancer Policy which is designed to speed up and streamline the promulgation of standards for potential cancer-causing substances and to resolve often-litigated issues will not directly impose cost burdens on industry. For these reasons, OSHA believes that economic analyses would be most usefully performed in the context of individual rulemakings.

B. DISCUSSION OF THE ECONOMIC FACTORS IN SPECIFIC ISSUES

The following sections discuss the economic issues relevant to the OSHA Cancer Policy in greater detail.

(1) Setting Priorities

While the OSHA Cancer Policy proposal required that substances be identified and classified as Category I and II toxic substances according to established scientific criteria, it did not specify exactly how priorities for regulation of substances within each category would be determined. However, OSHA recognized in the preamble to the proposal the need for "orderly handling" of potential carcinogenic substances and requested public comment on an appropriate procedure. (Ex. 1, 42 FR 51169–70). Extensive comments followed on the setting of priorities for regulating potential industrial carcinogens including specific proposals.

Many parties to the rulemaking stressed the importance of an explicit priority scheme for standards development. For example, the American Petroleum Institute stated that "OSHA must establish an effective means of prioritizing substances for regulatory action." (Ex. 252, p. 10)

Participants suggested specific options for establishing priorities. Several parties favored comprehensive quantitative priority systems that included detailed technical and cost information in addition to risk assessments for each substance. For example, Dr. Lave (Carnegie-Mellon Univ.), invited to testify by the API, recommended a priority system based on cost-effectiveness criteria. He stated that,

> "one indication of OSHA's success would be that it systematically formulated all regulations that would save a life for $50,000 or less, then later $100,000 or less, and so on. Such action would give OSHA a set of priorities which are sorely needed for dealing with NIOSH documents, petitions, and the thousands of potentially toxic substances. Using cost-effectiveness analysis to formulate priorities would provide a natural mechanism for defining how far OSHA should go to in enhancing worker health and safety." (Lave, Ex. 117, pp. 13–14).

Such a system would prescribe that OSHA select among potential substances for regulation those that offered the greatest improvement in

occupational health per dollar of society's resources. Dr. Zeckhauser also expressed similar views in his statement (S. p. 7) which are discussed in the analysis of the record section.

Other parties suggested less quantitative priority systems to direct resources at those substances creating the greatest apparent health risk. See, for example, NRDC, C. II–270, p. 23; AIHC. Recommended Alternative, § III–104–Q, pp. 41–42; RARG, Ex. 253, p. 21.

OSHA recognizes the need for establishing priorities for dealing effectively with the large number of candidates for scientific review and regulation as potential carcinogens. Decisions as to which substances to control and the order of regulatory proceedings can have important impacts on occupational health as well as on levels of industry and government expenditures. Theoretically, a systematic priority scheme can allocate more efficiently society's resources and provide maximum worker protection.

While OSHA has employed implicit procedures for determining the order of substances for standards development, OSHA agrees that an explicit system can provide industry and workers with improved information concerning future regulatory requirements, A predictable regulatory environment is more conducive to capital investment decisions that require discrete commitments of funds and hence longer range horizons. Improved industry planning can lead to the installation of hazard abatement controls that are more efficient, lower compliance costs and avoid disruptions in capital budgeting strategies.

OSHA also recognizes the role of improved information in stimulating innovation that could potentially provide more cost-effective and efficient controls than afforded by conventional techniques. An explicit priority system will augment the technology-leveraging effects of OSHA regulations which encourage new technology, process design, and product substitution. Finally, a priority system will increase workers' knowledge of potential health risks and their participation in the rulemaking process.

The final Cancer Policy will establish two priority lists for regulating potential occupational carcinogens. One list will include approximately ten (10) candidates for rulemaking as Category I potential carcinogens; the other approximately ten (10) candidates for rulemaking as Category II potential carcinogens.

Factors to be considered in setting priorities (where data is available) include: (1) the estimated number of exposed workers; (2) the estimated levels of human exposure; (3) the levels of exposure to the substance which have been reported to cause an increased incidence of neoplasms in exposed humans or animals; (4) the extent to which regulatory action can reduce not only the risks of contracting cancer but also other occupational and environmental health hazards; (5) whether the molecular structure of the substance is similar to the molecular structure of another substance which meets the definition of a potential occupational carcinogen; (6) whether there are substitutes that pose a lower risk of cancer or other serious health problems, or available evidence otherwise suggests that the social and economic costs of regulation would be small; and (7) other health and safety hazards and the actions being taken or planned by other governmental agencies in dealing with the same or similar health and safety hazards (§ 1990.132(b)). These factors together would include the extent to which health improvements can be achieved through regulation. The criteria will serve as rough guidelines to OSHA and the public in the development of priorities for the scientific review and regulation of potential carcinogens that maximize health improvements.

While the OSHA priority system includes as appropriate the assessment of cancer risk to workers resulting from exposure to carcinogens where data are adequate (§ 1990.111(j)), OSHA recognizes that quantitative risk assessment is at the frontiers of science and the results are crude or inexact because of the large number of uncertainties involved. The scientifc difficulties involved in performing risk assessment of carcinogens, using both epidemiological and animal data, are enumerated in detail in Section VIII.

Well conducted epidemiological studies of excess cancer risks in humans from industrial exposure are likely to be more reliable than animal test studies for the purpose of quantitative risk assessment. However, it is often difficult or impossible to get the data necessary to conduct epidemiological studies from which it would be possible to make reasonable estimates of risks. This generally requires a work force which can be traced and measurements or reasonable estimates of past exposures. The association between workplace exposure and disease is frequently obscured by the long-latency periods involved for industrial carcinogens. Confounding variables such as multiple causality (e.g. smoking), exposures to other chemicals and synergistic effects further complicate the quantitative estimation of human risks. Also, it may be difficult to extrapolate from risks measured at high exposure to risks at lower exposures. See the discussion in Section IV above as well.

Most potential carcinogens will be identified experimentally through animal tests. Animal studies present the major additional difficulty of extrapolating from high dose exposures in test animals to low dose exposure in humans. Section VIII above analyzes the difficulties, various scientific opinions and experience with past extrapolations.

Even where quantification of risk is possible, a wide range of uncertainty will still exist. For example, as discussed in Section VIII above, the estimates of risk from exposure to vinyl chloride vary by a factor of one million. Estimates of risks may understate actual risks by orders of magnitude. The high degree of uncertainty involved requires that cautious and prudent assumptions be utilized in performing such risk assessments. For many substances, only qualitative risk evaluations may be possible, particularly where animal data are involved.

The data constraints and large number of uncertainties involved in the estimation of human carcinogenic risks require a priority system that is sufficiently flexible to accomodate subjective information and policy judgments as well as information about the number of employees exposed, environmental exposure, the levels of exposure reported to cause excess incidence for neoplasms of various substances, and other factors to be considered as discussed above. Any priority list, therefore, cannot involve a strict numerical ranking scheme. The OSHA priority list will obviously determine only the approximate order in which rulemaking shall proceed and OSHA may select a substance not on the list. The final standard provides that OSHA will publish the priority lists in the **Federal Register** at least every six months and will periodically request information for the development of priorities. This process may lead to better data on priorities for regulation and elicit important information about newly-recognized hazards.

A "cost-effective analysis" approach to establishing priorities holds considerable heuristic appeal to some. Under cost-effectiveness analysis, potential regulatory actions would be undertaken according to the number of lives saved per dollar of expenditure. Where such information is available, OSHA will make use of it in setting priorities under the Cancer Policy.

However, OSHA does not believe that such analysis can be used as the primary basis for priorities-setting for several reasons.

First, OSHA believes that a more comprehensive cost-effectiveness priority system capable of providing meaningful estimates of relative costs per life saved cannot be formally developed given the data and resource constraints. The scientific difficulties in performing risk assessments in general at current exposure levels are magnified when health risks must be evaluated at alternative control levels.

Such analysis would also require estimates of compliance costs at alternative levels of control. OSHA's considerable experience with cost projections for occupational health standards suggests that such estimates are very controversial, time-consuming and as the vinyl chloride case indicates (discussed below in subsection 9), often highly inaccurate. Given their significance in such a quantitative ranking scheme, OSHA cannot accept Dr. Lave's suggestion for "back-of-the-envelope" cost calculations (Lave, Tr. 7007).

Cost-effectiveness analysis calculus would thus produce ratios of varying degrees of inaccuracy and comparability. In OSHA's view, the resulting estimates would produce numbers that are so highly speculative as to be essentially meaningless for comparison purposes. OSHA has opted for a more manageable priorities-setting approach that provides greater assurance that health resources are channeled at serious health hazards.

Second, a cost-effectiveness priorities scheme leaves unanswered how one evaluates quantitatively different health outcome possibilities (e.g., mortality versus morbidity) on a relative basis. Such calculations also ignore the subjective judgments necessary when cost and risk data are of differing degrees of uncertainty and where equivalent man-years saved estimates hide vast differences in death probabilities among different groups of workers.

Finally, cost-effectiveness ratios formally incorporate predetermined alternative control strategies and thus determine both the timing and stringency of control. Such analysis does not meet statutory requirements to set "the standard which most adequately assures, to the extent feasible . . . that no employee will suffer material impairment of health." (The Act, Section 6(b)(5)). This is discussed below.

OSHA, therefore, believes that consistent with the objectives of the Act, OSHA should set priorities to regulate substances in an order that maximizes the health benefits arising from such regulation. The OSHA priority system will include quantitative risk assessments where data are adequate and consider information on the social and economic costs of regulation as appropriate. The priority system included in the final Cancer Policy will thus provide better assurance that societal resources are concentrated on substances likely to produce the greatest health impacts in future regulations issued pursuant to this policy and improve the regulatory decision-making process. See Section IX–G of this preamble for a discussion of other non-economic aspects of the priorities issue.

(2) Automatic Regulatory Requirements and Prescribed Timetables

The OSHA proposal provided that following a brief comment period, upon initial classification of a substance as a Category I toxic substance, there would be the automatic issuance of an Emergency Temporary Standard (ETS). The ETS would have required the identification of exposed employees, monitoring of exposure levels, medical examinations, and immediate reductions in exposures to the lowest feasible level. Simultaneously with the issuance of the ETS, a proposed permanent standard was to be published, public comments invited and a hearing scheduled. At the end of the rulemaking, if the Secretary determined that classification of the substance was correct and not rebutted, a final standard was to be issued. Pursuant to Section 6(c) of the Act, the final standard would be promulgated within six months from issuance of the emergency temporary standard. Permanent standards were also required for Category II Potential Carcinogens within a specified timeframe. OSHA received public comments concerning the provisions for automatic regulation of all workplace carcinogens within prescribed timeframes.

Some participants in this proceeding supported the automatic issuance of emergency temporary standards for Category I Potential Carcinogens. For example, the NRDC, OCAW, EDF and UDF argued this was the correct approach in their joint post hearing brief (Ex. 268). It has been argued by those in favor of the automatic ETS provision for Category I Potential Carcinogens that the potentially serious health consequences associated with evidence of proven carcinogenic hazards in workplaces, necessitated immediate reductions in exposure levels and commencement of environmental and biological monitoring and investigation of engineering controls. Further, immediate issuance of an ETS would not prove unduly disruptive because of the flexibilities built into the proposed ETS model standard requirements.

Other participants to these proceedings commented on the potential disadvantages of the automatic requirement for issuance of ETS standards. They contended that it would not be necessary in all circumstances and questioned the legality of the provision. See Ex. 252, pp. 84–89; Ex. 251A, pp. 234–7.

Section IX–4 has a detailed discussion of the questions presented by the automatic issuance of ETS's and the changes OSHA has made from the proposal. OSHA has carefully reviewed the evidence on these issues. In summary, OSHA recognizes the need to establish a rational priority system to assure an orderly and effective approach to the scientific review and regulation of potential occupational carcinogens. The automatic issuance of ETS's would make it difficult for a priority system to operate. Thus, the final Cancer Policy does not contain a requirement for automatic issuance of an ETS for Category I Potential Carcinogens. OSHA believes that prudent utilization of its resources requires the flexibility to target regulatory actions where they are most needed. OSHA will continue to issue emergency temporary standards as appropriate pursuant to Section 6(c) of the Act. This flexibility will also allow OSHA to propose permanent standards for substances without first issuing emergency temporary standards, thus assuring more efficient allocation of public and private resources.

(3) Model Standards

The OSHA proposal contained three model standards: an emergency temporary standard for Category I Toxic Substances, a permanent standard for Category I Toxic Substances and a permanent standard for Category II Toxic Substances. These proposed model standards included detailed requirements for monitoring, medical surveillance, housekeeping, hygiene facilities, shower rooms, lunch rooms, recordkeeping, etc. (Proposal, Ex. 1, 42 FR 54187–95). It was to be an issue "whether the toxic substance has unique properties or uses that make the specific protective measures of the proposed (model) standard inappropriate or infeasible." (Proposal, § 1990.113, 123). But the Secretary was "to issue a final standard which shall follow the format and content of the model standard. . . . Any deviation, addition or change from that format and content shall be explained, together with the

reasons therefore." (Proposal § 1910.114, 124)

Discussion in the Record focused on both the role of model standards and specific requirements. Industrial hygiene experts generally supported the need for the provisions as auxilliary controls under most circumstances. The Record on these questions and on the non-economic reasons for the changes from the proposal to the final regulation is analyzed in detail in Section X.

Economic criticism of the role of model standards centered on concerns that relatively strong presumptions in favor of the detailed provisions of the model standards could lead to frequent inclusion of provisions for specific carcinogens that are ineffective as worker protection measures but impose substantial cost burdens on the regulated industry.

For example, the RARG stated:

"OSHA proposes that detailed model standards be triggered by the classification of a substance as a carcinogen. Because such substances can vary widely in such aspects as their potency, chemical state, primary route of entry, and production processes, the RARG report recommends that the model standards be kept flexible. The detailed requirements for certain means of compliance, certain types of hygienic and eating facilities, for specific housekeeping practices and for monitoring of the workplace air may not always be appropriate or cost-effective." (Ex. 253 p. 8, see also pp. 30–35).

A number of other participants made similar comments. For example, API stated that:

"The need for flexibility is demonstrated by the record of the proceeding which reveals considerable diversity among substances, workplaces and protective measures. Thus potential workplace carcinogens may vary considerably in carcinogenic potency, chemical state (liquids, gases, solids, dusts), primary route of entry, levels and variations in levels of exposures, specificity of tumor sites, the appearance of detectable precancerous conditions and in many other ways. Moreover the cost, form and availability of resources for controlling exposures, monitoring, medical testing and achieving other protective goals can vary substantially from one substance to another, and from one workplace to another." (Ex. 252, App. 6, p. 6)

After considering the Record, OSHA has decided to substantially increase the flexibility of the model standards provisions in order to accommmodate potential diversities among substances in chemical properties, routes of entry, process types and other characteristics relevant to health risks. For example, there appears to be less need for showering provisions in the case of gases than for dusts. The monthly monitoring provision of the proposal may also prove unnecessary in specific situations. (See Lave, ex. 117, pp. 19–33, but compare AFL–CIO, ex. 261, pp. 99–102).

The final Cancer Policy provides that the model standard provisions will serve as guidelines to be followed when appropriate. Certain general types of requirements will be presumed to apply, such as monitoring and medical surveillance except where circumstances so warrant, but the detailed requirements are to be determined on a substance-by-substance basis in the individual rulemakings. See the extensive discussion of these changes in Section X. The use of model standards as guidelines eliminates the strong presumptions in favor of specific, detailed, and occasionally costly industrial hygiene provisions. Specific regulatory provisions will now be tailored to the needs of the particular substances regulated.

The RARG (Ex. 253, pp. 8, 34) and several other parties recommended that OSHA give special recognition to "performance" standards. OSHA believes that the changes in the role of the model standards and in the design of specific provisions will improve the flexibility and performance-orientation of regulatory provisions for individual substances.

In conclusion, the modifications adopted in the model standard provisions will substantially improve the cost-effectiveness of individual substance regulations. The flexibility introduced in the model standards will avoid requirements for standard provisions that do not improve worker health protection.

(4) Action Levels and Percentage Exclusions

The Cancer Policy proposal did not specifically provide for action levels or percentage exclusions. As discussed in depth in Section X.B.I. an action level is an exposure substantially under the maximum permissible exposure limit, below which few, if any, regulatory requirements apply. For example, the arsenic standard (29 CFR 1910.1018) contains a 10 $\mu g/m^3$ permissible exposure limit with a 5 $\mu g/m^3$ action level. For exposure levels above 10 $\mu g/m^3$, the full requirements of the regulation are applicable. Exposures between 5 $\mu g/m^3$ and 10 $\mu g/m^3$ require only medical and exposure monitoring provisions. Below the 5 $\mu g/m^3$ action level, the only requirement is for initial environmental monitoring if there is a possibility that arsenic exposure might exceed the action level.

A percentage exclusion exempts employers with regulated substances present as small fractions of other substances from most regulatory requirements. For example, employers who have ethyleneimene (29 CFR 1910.1012) present as less than 1% of a mixture with another substance are not covered by that regulation.

Action levels and percentage exclusions are designed to avoid unnecessary regulatory requirements at exposures substantially under the permissible exposure limit (PEL). Both may exclude from coverage certain workplaces well under the PEL. In addition, action levels provide for some necessary control precautions as exposures approach the PEL. Medical surveillance and environmental requirements can indicate situations requiring corrective action.

OSHA's proposal did not explicitly include an action level or percentage exclusion because it was believed that substantial variations in chemical properties and routes of entry (e.g.; dermal absorption versus inhalation) made difficult generalizations about these concepts. However, OSHA had found action levels or percentage exclusions appropriate in most of its prior regulations of carcinogenic agents. (See the 13 carcinogens regulated at 29 CFR §§ 1910.1003–1910.1016, vinyl chloride at § 1910.1017, arsenic at § 1910.1018, benzene at § 1910.1028, and acrylonitrile at § 1910.1045).

Parties to the rulemaking generally criticized the absence of action levels and percentage exclusions concepts, arguing that failure to incorporate such provisions could, in many circumstances, greatly inflate the costs of compliance without providing additional health protection to employees. API recommended inclusion of the action level concept in the model standard for Category I potential carcinogens (Ex. 252, app. C, pp. 25–27) stating:

"While provision for an action level may not always be appropriate, a definition should appear in OSHA's model standards to raise the issue for consideration in individual cases by OSHA and the public." (pp. 26–27).

AIHC also argued that action levels and percentage exclusions should generally be included in carcinogen standards. Regarding their potential advantages, AIHC stated:

"By fixing a mixture cut-off, the number of regulated workplaces will drop dramatically without in any way endangering employee health * * *".

"Similarly, the use of an action level makes it possible to reduce dramatically the cost of compliance since monitoring and medical surveillance, which make up a large part of

the costs of compliance, will be reduced." (Ex. 251A, p. 249).

While OSHA believes that serious methodological flaws in the Snell Report (S. III–104 R&S, see discussion below) invalidate their cost of compliance findings, the Snell report consultants agreed that inclusion of an action level concept in their costing assumptions would have clearly lowered their compliance costs estimates (Tr. 3672–3673). For example, an estimated $1 billion capital cost item in the "other industry" segment of the vinyl chloride industry would have been completely eliminated. (Tr. 3672–73). They also stated that an action level for tetracholoralthylene would "substantially lower the $331 million compliance costs projected for regulation of this chemical" (Tr. 3675).

Other participants also expressed equally strong support for the establishment of an action level concept. Dr. Robert Harris, (S. 20), a recognized expert in workplace monitoring asked to testify by OSHA, recommended that a definition for action levels be incorporated in the model standards. The AFL–CIO also approved inclusion of action levels to the extent that the model standards did not define specific values, but allowed for case-by-case determination of appropriate lower limits (Tr. 5713, Ex. 261, pp. 98–99).

OSHA agrees that inclusion of action levels or percentage exclusions in regulations of most carcinogens can, in appropriate cases, potentially create large costs savings without impairing worker health protection. The final Cancer Policy contains definitions of action levels and percentage exclusions to be applied where appropriate.

(5) Suitable Substitutes

The Cancer Policy proposal included a provision that would set a "no occupational exposure" level for confirmed carcinogens where a suitable substitute existed. This provision would not "ban" a carcinogen where a suitable substitute existed, but would encourage substitution by setting a very low exposure level. The final Cancer Policy retains this concept but with substantial modifications designed to meet technical and economic criticisms. Section XII–B of this preamble discusses at length the reasons for the proposal, public comments received, and the rationale for retention of the concept in changed form.

OSHA is maintaining the "suitable substitutes" provision in the final Cancer Policy based on the generally accepted scientific principle that there is no existing method to reliably determine a safe level of exposure to a carcinogen (See Section V 10). Substitution (if feasible) is by definition the most protective compliance strategy since it eliminates the hazard without extensive control devices and avoids the possibility of unintended exposures caused by equipment malfunctions. The AFL–CIO (Ex. 261), United Automobile Workers (Tr. 5725), the Natural Resources Defense Council (C. II–270, p. 38, Ex. 268, p. 40; Tr. 6316–19), and the Health Research Group (Tr. 6352–54) strongly recommended that OSHA retain the suitable substitutes requirement for these reasons.

However, a number of other participants contended that OSHA did not adequately define the term "suitable substitutes" in the proposal. OSHA intended that this provision be used only in cases where the substitute for the potential carcinogen was relatively effective technically and where the costs of substitution were feasible. It was pointed out, however, that the general language in the proposal could lead to applications of the suitable substitutes provision in circumstances where substitution was technically possible, but not nearly as effective, or where costs of substitution were not feasible. For example, AIHC argued in its post hearing brief that "substitution . . . would be dramatically costly and disruptive if forced where no technological alternative now exists . . . The huge irreversible shifts in the economy from such a price change or ban underline the great economic significance of this issue." (Ex. 251A, p. 69).

The AIHC utilized a study done by Charles H. Kline & Co. for Shell Oil Company (S. III–83) to support this contention. The Kline study assumed a substitution scenario banning the use of benzene, ethylene oxide and vinyl chloride. No statistical cost data was collected with which to perform a market analysis predicting the direct compliance costs and economic effects of substitution. Instead, the study relied on interviews with various industry officials (sometimes identified see p. 9, usually not see p. 12) to solicit responses as to whether such a policy would put their company "out of business" (p. 9) or create "sheer disaster" (p. 12). Kline then reviewed basic trends in production, price, and employment data. Normally, these trends would be applied to projections of cost increases due to regulation through input-output analysis to predict the economic effects. With no data base however, the Kline study could only qualitatively determine their numerical assessments of economic impacts. The study results, not surprisingly, suggested large price increases and reductions in output and employment for various industries under the assumed scenarios.

In addition to the non-rigorous methodology and questionable survey techniques employed, the Kline study failed to establish reasonable scenarios concerning future regulatory outcomes under the suitable substitutes provision and to evaluate cases where substitution lowered costs. The failure of the study to establish parameters that properly reflect the scope of OSHA's substitution policy, invalidates use of the results as even crude indicators of likely regulatory impacts. Shell accepted that the "intent here was really to show what the extreme could be." (Tr. 5586).

Previous OSHA experience with such studies leads to similar conclusions. For example, before the issuance of OSHA's vinyl chloride standard, Arthur D. Little, Inc. submitted a study (Ex. 69), similar to the Kline analysis for vinyl chloride, which concluded:

> "The companies in the PVC resin industry have stated that they would be unable to meet the newly proposed non detectable tolerance standard and its enforcement would force the shutdown of all PVC resin plants in the U.S. . . .
>
> "Summarizing the conclusions of this report, we find that an immediate shutdown of all PVC resin plants in the U.S. and the subsequent unavailability of PVC resin would result in a loss of 1.7–2.2 million jobs in consuming and related industries and a loss of domestic production value of $85–90 billion annually." (p. 1).

Although OSHA set a 1 ppm level, then considered the lowest level detectible with available sampling techniques, none of the predicted consequences occurred. Retrospective analysis indicated that after the vinyl chloride regulation was issued, the growth trend in production of PVC continued at 8–11 percent annually, with the exception of the 1975 recession year. There was no net loss of employment although 2 of the oldest and least-efficient plants (out of 23) did shut down, while production costs increased only 6 percent. (Ex. 70)

In view of the weaknesses of the Kline study and other examples placed in the Record (see the discussions submitted by the refractories industry and others in Section XII–B–5), as well as agency experience with similar studies, OSHA believes that the evidence fails to substantiate predictions of economic disaster stemming from the OSHA suitable substitutes provision.

Nevertheless, OSHA is sensitive to the concerns expressed of possible severe economic consequences resulting

from improper application of a broad suitable substitutes provision. OSHA has therefore clarified the suitable substitutes provisions in the final regulation, to make explicit its intended policy that technological and economic feasibility considerations be applied to determinations of whether suitable substitutes exist. The final regulation requires that the technical feasibility of the possible substitute, including its relative effectiveness, be taken into account. The economic costs of substitution must also be considered in determining feasibility, including direct compliance costs and the time needed for raising capital and orderly changeover of production facilities. The final regulation requires that evidence on the relative safety of potential substitutes be carefully analyzed. This meets AIHC's concern that the suitable substitutes provision might be utilized when the substitute itself is actually more hazardous.

OSHA believes the modifications in the final suitable substitutes provision meet the economic concerns of industry representatives. These changes will make explicit reasonable policies regarding determinations of whether a suitable substitute exists or whether substitution is infeasible. However, OSHA has retained the preference for substitution as the most protective compliance strategy for carcinogens where substitutes are found suitable.

(6) Engineering Controls

The final Cancer Policy maintains the preference for engineering controls and work practices to reduce worker exposure to potential occupational carcinogens. OSHA's policy reflects the much greater relative-effectiveness of engineering and work practice controls and the frequently greater failure rate of personal protective equipment.

Section X.B.7 of the preamble provides a detailed discussion of alternative technological approaches to controlling carcinogens and concludes that the greater relative-effectiveness of engineering and work practice controls is substantial. The following sections briefly summarize the evidence.

While expressing a general preference for engineering controls, some parties recommended that greater reliance be placed on respirators as a feasible and cost-effective alternative to engineering controls in certain situations. API stated that while agreeing that engineering and work practice methods are generally preferable, "the record shows that engineering or work practice controls will be plainly cost-ineffective in situations even though they are technologically and financially possible." (Ex. 252, App. B, p. 247). The AIHC (Ex. 251A, p. 274) and the American Iron and Steel Institute (Ex. 219, pp. 38–40) expressed similar views.

Dr. Zeckhauser also suggested that personal protective devices be considered acceptable primary control strategies when "cost-effective." He stated,

> "What I am suggesting—and I am not an expert on respirators or engineering controls—is that we use the most cost-effective means of reducing exposures where that is available. If respirators are effective and they protect workers at the same cost better than engineering controls, then I would say we should have respirators." (Tr. 4353.)

Nearly all industrial hygiene experts expressed the opposite position; namely, that personal protective devices should serve only as secondary lines of defense. See the testimony of Mr. Held (Univ. of Cal., Lawrence Livermore, Tr. 2683), Mr. Soule (S. V–15, p. 8), Mr. Douglas (Univ. of Cal., Los Alamos, S. V–19, p. 3), Mr. Holaday (S. V–20, p. 3) and Dr. Billings (Johns Hopkins, S. V–31, p. 13).

Other industrial hygiene experts also recommended against primary reliance on respirators. Mr. Thorpe, testifying on behalf of API, stated:

> "And as soon as you say respirators, everybody gets a bit claustrophobic about the idea of a man working eight hours with a mask on in a horribly dusty environment; and they are naturally repelled by that. And I do not think there is anyone in his right mind that is going to advocate that a man be required to work eight hours a day, five days a week in that kind of situation." (Tr. 4514.)

Dr. Langer (Dow), Tr. 5118; Dr. Janus (Hooker Chemical), Tr. 4161; Dr. First (AIHC), Tr. 6852–3; and Dr. Jaeschke (Stauffer), Tr. 6798, expressed similar views.

OSHA has carefully reviewed all relevant aspects of the Record on this issue. OSHA believes that the substantial weight of the industrial hygiene evidence supports the continued primacy of engineering and work practice control strategies.

OSHA accepts that in some circumstances, respiratory protection may be cheaper than engineering controls. However, simply because a particular technological approach is cheaper does not mean it is "cost-effective."

The cost of a respirator control strategy is frequently analyzed only in terms of capital outlays. However, in addition to capital costs, a comprehensive respirator program would require more frequent and careful monitoring and medical surveillance. This would involve increased recordkeeping, employee notification, and observation of monitoring, as well as worker education and training. Employers would also have to provide a program of tests to demonstrate and ensure fitting. OSHA would have to ensure compliance through increased inspection activity. All of these factors contribute to substantial administrative costs involved in implementing a comprehensive respirator program that must properly be included in estimates of the relative costs of respirators compared to engineering and work practice controls.

Further, there is substantial evidence that even a comprehensive respirator program may not provide adequate protection because of reliability problems. In addition to technical efficiency problems, difficulties are frequently encountered in preserving face fits, and in installing, cleaning, and replacing filters.

Communication is also difficult while wearing a respirator. Any jaw movement can break the facepiece-to-face seal and cause respirator leaks. Claustrophobia, anxiety and general physical discomfort may also limit the effectiveness of respirators.

Cost-effective approaches are only meaningful when alternative technologies are of comparable reliability in providing worker protection. Quantification of the risks associated with alternative control strategies is at the frontiers of science. This problem is significantly magnified when the alternative control strategies involved widely-differing degrees of reliability of both a technical (theoretical efficiency) and in practice nature. In addition to the relatively greater failure rate of respirators, a cost-benefit analysis would have to adjust benefit (reduction in risk) estimates to reflect the extent of non-supervision, bad-fitting, and other reliability factors. Conventional cost-benefit analyses in favor of respirators have not made such adjustments. Such risk estimation in practice would be difficult and highly uncertain given the current state-of-the-art of risk assessment techniques and the heavy dependence on predictions of employer behavior. Furthermore, the administrative costs necessary to insure a respirator program of comparable effectiveness to engineering controls would likely be substantial, thereby lowering the benefit to cost ratio (even assuming equal reliability).

Finally, as pointed out in Section X.B.7., the OSHA requirements for engineering controls are not as inflexible as industry representatives suggest. For example, Sections 1990.151 and .152 permit the use of respirators in maintenance or similar intermittent

operations where engineering controls are not feasible.

(7) The Role of Economics in Setting Exposure Levels

The proposal followed the approach used by OSHA in past regulations to set permissible exposure levels for carcinogens, requiring that exposures to Category I toxic substances be reduced to the "lowest feasible level." Several parties suggested a formal integration of quantitative risk assessments with cost data in determining appropriate levels of hazard control.

To understand the differences in these approaches, it is useful to clarify the Secretary's decision-making process and differentiate that from other approaches which rely upon traditional cost-benefit analysis.

The Secretary's decision-making process under OSHA first involves an evaluation of the adverse health effects which result from exposure to a toxic substance, using disease epidemiology and toxicological evidence and exposure monitoring data, where available. Health assessments help to determine the overall magnitude and severity of occupational disease problems. They assist in determining the need for regulatory actions (prioritization); in evaluating properties of exposure to given health hazards (i.e., routes of entry, chemical state, etc.); and in relating the extent of exposure risk to carcinogenic agents in specific industrial settings (i.e., processes, presence of co-contaminants, intensity of exposure etc.). Many aspects of such health evaluations are necessarily qualitative in nature because of data limitations and the large number of uncertainties involved.

OSHA also conducts technology assessments which include an evaluation of existing control technology and of the regulated industry's capability to develop or purchase control technology, to redesign its production technology, and to develop and utilize substitute products or equipment. The economic consequences of alternative technological approaches are one factor in the analysis, along with an evaluation of both the technical reliability and comprehensiveness of protection of alternative control strategies.

As part of this generic approach to regulation of carcinogens, OSHA has concluded that quantitative risk assessments, where available, may be utilized as a factor in establishing priorities for regulation. Health assessments of both a quantitative and qualitative nature are also relevant in rulemakings for evaluating control needs for specific industries and processes; in the design of standard provisions (e.g., the need for action levels, biological and environmental monitoring frequency, etc., and in assessing likely health outcomes from regulation.

The determination of feasibility includes an assessment to determine the lowest exposure level generally achievable by the affected employers through engineering and workpractice controls. This level takes into account that in some locations where control is difficult, respiratory protection may be used to supplement engineering controls. The cost of achieving this level are compared with the economic capabilities of affected industries. The regulation issued is designed so as to be achievable from an economic perspective. Some factors which the agency takes into account in assessing economic feasibility where appropriate include the costs of best available control technology and work practices; exposure levels achieved by industry leaders; costs of new and improved control technology which is "looming on the horizon"; the ability of each affected industry and the national economy to bear financial costs, among other factors.

OSHA's determination of feasibility has been narrowly construed by some to be restricted only to matters determining the economic affordability of controlling exposure of the substance under consideration. However, the Department of Labor in the brief to the Supreme Court on benzene in *Marshall v. American Petroleum Institute* has stated:

"Second, 29 U.S.C. 655(b)(5) comes into play after the Secretary decides to issue a new standard. Thus, if a rulemaking record affirmatively demonstrates that an existing standard is highly protective and that imposing a more stringent standard would threaten the industry's ability to respond to other health hazards without significantly improving health protection, the Secretary has discretion not to issue the standard or to delay regulation until more immediate hazards are addressed."

"Furthermore, the Secretary has never asserted that he is precluded from considering (where there is some reason to believe it is so) whether the cost of a standard is sufficiently large that the affected industry will be unable to respond effectively to future health hazards. If that situation were to arise, the statutory phrase 'most adequately assures, to the extent feasible' (Section 655(b)(5)) is sufficiently flexible to allow the Secretary to take into account in setting a standard the need for the industry to meet future threats to employee health. In short, there is no realistic basis for respondents' hyperbole that the Secretary's regulatory approach will lead to a severe misallocation of finite occupational health resources."

Several of the major industrial participants advocated that an "efficiency-based" approach be used to determine permissible exposure limits. Their approach would estimate risks to workers and compliance costs at alternative levels of exposure for each substance regulated. The cost and risk reduction estimates at various exposure levels of substances would be integrated into a framework for achieving maximum worker protection per dollar of health resources expended. Efficiency criteria would determine the stringency of control technology mandated. Exposure levels would be set higher (lower) than the lowest feasible level defined by OSHA depending on whether the costs of hazard abatement at the margin were higher (lower) than the value of preserving life or preventing disease.

OSHA has carefully examined the evidence in this Record on alternative approaches to regulating toxic chemicals. The final Cancer Policy retains the OSHA proposal's approach to standards setting in conjunction with an explicit priority system to direct regulatory efforts at more serious health hazards. It requires that exposure to confirmed carcinogens be reduced to the lowest feasible level, but adds language to make explicit OSHA's intent to take into account technological and economic considerations in determining feasibility.

OSHA believes that this decision-making process reflects not only the clear legislative mandate discussed below, but also avoids technical and methodological problems which render alternative decision rules inappropriate. Specifically, OSHA has determined that an approach to setting permissible exposure limits based on efficiency criteria alone would be inappropriate for three reasons.

First, a cost-benefit or cost-effectiveness approach hinges critically on the ability to develop reliable numerical estimates of cancer risks. Risk assessment techniques, particularly for carcinogens, are too crude and unreliable to permit the depth of analysis necessary for estimating the extent of health impairment associated with different exposure levels. (See Section VIII for an extensive discussion of this issue.) OSHA believes that while quantitative risk estimates can be a useful element along with other factors,

in setting priorities and in examining likely health outcomes from regulation, estimates with wide variations that may understate cancer risks by many orders of magnitude are not sufficiently instructive for setting control levels. Cancer is an irreversible disease leading to death with no demonstrated threshold or safe level and thus requires a highly protective regulatory approach. Uncertainties in cost estimation introduce further distortions into comparisons of costs and health benefits which render cost-benefit ratios inappropriate as the basis for decision rules for determining levels of worker protection.

Second, as a matter of policy, decisions based on efficiency criteria are not appropriate because they ignore equity considerations. The economic savings from less protective regulation accrue to industry in the form of higher profits and to consumers through lower prices. But the costs are borne by workers through increased industrial illness and death rates.

Finally, OSHA believes that correct interpretation of its legislative mandate requires the agency to set the lowest feasible level for those substances where no safe level can be shown.

The following sections outline several alternative approaches based on formal integration of risk assessment and technological/economic evaluations and the methodological and legislative bases for OSHA's determination that alternative decision rules for determining acceptable exposure levels are inappropriate.

Industry representatives recommended that numerical estimates balancing social costs and benefits from the primary basis for the setting of standards for individual carcinogenic agents. These parties argued that the OSHA Cancer Policy as proposed was designed to achieve a risk-free society, and that this is an undesirable goal because it is impossible to achieve and wasteful of economic resources. Industry participants contended that cost-benefit analysis would ensure maximum health protection because of limitations in the total health resources available for improving workplace health.

Dr. Zeckhauser, for example, argued that workers and society at large, would suffer if health expenditures are not efficiently allocated because fewer cases of cancer would be prevented (Tr. 4410). Similarly, Dr. Lave indicated that since society is willing to spend only some of its resources on health protection, it must attempt to determine the value of possible purchases in order to make intelligent expenditure decisions." (Lave, Tr. 6993).

The AIHC summarized the views of many industry participants in their post-hearing brief (Ex. 251 A, pp. 22–230). They concluded:

"AIHC believes that the record strongly supports the conclusion that OSHA should undertake a cost/benefit analysis as part of the regulatory process to determine the level of control. This may not necessitate an elaborate formal cost/benefit analysis but it does mean that OSHA will have sufficiently identified the societal costs and benefits that it can more reasonably determine an acceptable level of risk—the reasonably necessary level—in setting particular standards." (Ex. 251A, p. 230)

The methodologies employed in cost-benefit or cost-effectiveness analysis have been discussed at length in the section on analysis of the record. They will only be briefly summarized below.

Conceptually, it may be appropriate to tally the costs and benefits to society at large associated with an investment project. Under this cost-benefit framework, if benefits exceed costs, there is a net social benefit and the project should be undertaken. Regarding occupational health investments, estimates of the costs of compliance at a particular control level would be compared to the permanent or long-term benefits of improved occupational health defined as the costs of nonregulation. Exposure levels would be lowered only the extent that the benefits of improved health (including extended longevity) exceed hazard abatement costs; otherwise, resources would be more efficiently spent elsewhere.

Dr. Wilson advocated such a cost-benefit approach to regulating chemical substances with risks of death between 1/100 and 1/100,000 per year. Controls would be installed only to the extent that they save one life for every $1 million in expenditures, his implicit estimate of the value of human life. Other parties to the proceeding recommended cost-effectiveness analysis as a procedure for setting standards. (It should again be noted that the term "cost-effective" has two meanings. Drs. Lave and Zeckhauser use it as a noun to describe a formal mathematical analysis which is explained in the next paragraph. Cost-effective also may be employed as an adjective to refer to the achievement of a predetermined degree of health protection with the least expenditure of society's resources.)

Cost-effectiveness analysis avoids some of the human valuation problems attendant with cost-benefit analysis. Under this framework, estimates of costs and risk reduction at various exposure levels for different substances would be expressed in terms of lives saved per dollar of health expenditures. OSHA would proceed to regulate in order each chemical to the level which would save the most lives per dollar. Some chemicals would undergo more than one regulatory proceeding. For example, suppose that there are 3 carcinogenic chemicals. Controlling chemical X from 500 to 100 would save 1 life per $100,000; from 100 to 20, 1 life per $500,000; and from 20 to 1, 1 life per $2 million. Controlling chemical Y from 200 to 50 would save 1 life per $200,000; from 50 to 10, 1 life per $750,000; and from 10 to 2, 1 life per $5,000,000. Controlling chemical Z from 10 to 1 would save 1 life per $800,000; and from 1 to 0.1, 1 life per $1 million.

For this hypothetical case, Drs. Zeckhauser and Lave would recommend the following governmental response. First, OSHA would regulate X from 500 to 100, then Y from 200 to 50, then Z from 10 to 1, then X from 100 to 20, etc. Regulation would not continue until all possible regulatory actions were exhausted, but would stop at the point where the cost to save one life was greater than the risk that society deemed acceptable. Cost-effectiveness analysis was to be further expanded to include alternative control strategies, noncarcinogenic health effects, and even nonoccupational health actions (highway safety, hospital construction, etc.).

A cost-effective or cost-benefit approach to setting permissible exposure levels would balance control costs and predicted benefits at the margin. Dr. Zeckhauser explained marginal analysis and its use in setting exposure levels as follows:

"[I]t is important to determine not only how much is achieved on average for a particular level of expenditure but how much is achieved at the margin . . . We might look at a standard that reduces exposure by an amount X at an expenditure of $100 million. The gain may seem worth it. But the gain at the margin may be rather minimal. What if we would achieve a reduction of 99% of X for an expenditure of merely $50 million? Well, that last small reduction in exposure would be costing a very great deal."

Under this incremental approach, that last unit of protection would be required only when it is cost-effective.

AIHC and API submitted lengthy post hearing briefs (exs. 251 and 257 respectively) in support of cost-effectiveness and cost-benefit analysis for the setting of standards as well as priorities. They recommended that economic and risk assessments be performed for each proposal. This information would then be formally

integrated into a cost-benefit or cost-effectiveness analysis. Under this approach, the lowest feasible level would not automatically be set for Category I carcinogens, rather the cost and benefits would be used as part of the regulatory process to determine the "reasonably necessary" level of risk.

While cost-benefit or cost-effectiveness analysis can illustrate the nature of economic trade-offs involved under various regulatory alternatives, they say little about how much occupational health improvement society can afford or is willing to pay for. Wilson's recommendation attempted to define an overall objective function for determining acceptable levels of risk. Using comparative risk analysis, Dr. Wilson calculated single-point estimates of risks which individuals voluntarily (engaging in certain sports activities) or involuntarily live with (pedestrian in a motor age). For example, he calculated that some individuals voluntarily accept a risk of death of 1/1000 per year of activity to engage in risky sports such as auto racing and rock climbing. Smokers "voluntarily" accept a level of risk three times higher. People "involuntarily" accept a risk of 1/5000 per year from motor vehicles—his highest estimate of involuntarily accepted life-style risk. The highest fatality rates that Wilson reports among occupational groups in the workforce presently are approximately 1/1000 per year for coal miners, railroad workers and firefighters. However, the risk of death for coal miners from work-related causes approaches 1 death per 100 annually when fatalities from black lung disease are included.

He argued as an appropriate benchmark for risk reduction that OSHA not attempt to lower occupational risks below other voluntarily accepted risks levels. (S.III–104D, p. 38). He used his estimates of non-occupational risks voluntarily accepted or involuntarily lived with to develop risk categories for structuring occupational regulatory actions.

Dr. Wilson recommended different regulatory responses for risks in excess of one death per 100 employees per year (regulation irrespective of cost) and for risks below one death per 100,000 annually (no regulation). For occupational risks of death between these boundaries, cost-benefit analysis would determine the reduction in risks. (See discussion in the subsection on analysis of the Record for further detail).

While these efficiency approaches may be intrinsically appealing as "objective" numerical decision rules, they are inconsistent with the Act. In addition, they are beset, in practice, by serious technical and methodological problems that expose their subjectivity and undermine their appropriateness as the decision mechanism for determining exposure levels.

The following sections examine the analytical and legislative difficulties underlying such analyses.

First, OSHA believes that the use of cost-benefit and cost-effectiveness analysis to set exposure levels in a largely mechanical fashion is inappropriate because the calculations involved are crude and carry serious potential for misleading health determinations. Cost-benefit and cost-effectiveness analysis depend crucially on the reliability of risk and cost estimates for their legitimacy, since relationships between a series of these numerical estimates define the set of substances for regulation and the stringency of control levels.

The Record contains extensive comments on the difficulties involved in performing cancer risk assessments. There is intense scientific controversy on the issue of the reliability of risk estimates, particularly for carcinogenicity. Some scientists and expert committees contend that risk can be confidently estimated, while others believe that risk assessments are likely to be highly inaccurate. Their various views on differences in quantitative responses between test animals and humans, and methods of extrapolating from high doses to low doses are analyzed in Section VIII.

Even strong proponents of risk assessment recognized the significant difficulties inherent in relating disease incidence to different exposure levels. Dr. Lave, testifying on behalf of the API stated, "It is generally difficult to estimate the extent of the decrease in the probability of accident or disease when a safety device is added or exposure levels are lowered. Indeed some of the questions are almost impossible to answer in principle since they involve low exposures over prolonged periods to small groups." (S.III–125, p. 10.) Dr. Zeckhauser also accepted the enormous difficulties entailed in estimating the number of lives saved through a specific reduction in exposures, but argued that such estimates must be made despite their crudeness.

A careful review of the scientific evidence has led OSHA to conclude that risk assessments for carcinogens are in general highly inaccurate and can not provide a sufficiently reliable basis for determining levels of worker protection. The ability to perform quantitative risk assessments for carcinogens differs from classic toxins because there is no known safe level for exposure to carcinogens. Risk assessments must be made for exposure levels where data are usually unavailable. While extrapolation from historical statistical bases is the conventional technique for computing such estimates, risks for nearly all industrial carcinogens must be identified experimentally because of the long 20–40 year latency periods between exposure and onset of disease. For most carcinogens, such assessments will require extrapolations from high dose animal tests to much lower exposures in human populations.

As a result, unlike other toxic substances, no single number with a small range of uncertainty can be found to represent a safe level. For carcinogens, the "best estimate" from standard linear no-threshold interpolation represents only a beginning in the assessment of risk. Such a single number "best estimate" may understate or overstate actual cancer risk by orders of magnitude. The actual risk may be 10–10,000 times larger or smaller than the predicted risk.

Two examples illustrate the enormous range of valid estimates of risk for carcinogens which are possible under different, but plausible assumptions. Estimates of risk for vinyl chloride at 1 ppm vary by a factor of 1 million, from a life-time risk of exposure of 1/100,000,000 to 1/100. For saccharin, estimates of excess bladder cancer cases derived from animal data as a result of lifetime saccharin use range from .001 per 1,000,000 exposed to 5,200 per 1,000,000 exposed. An estimate based on epidemiological data predicts 15,000 bladder cancers per 1,000,000 exposed. The range in possible defensible estimates is over ten million (See Section VIIIc8).

OSHA believes that crude estimates of risk exhibiting such wide variation are not sufficiently instructive to form the basis for setting exposure levels. Cancer is an irreversible disease commonly leading to death with no known safe levels of exposure and thus requires a high level of protection.

The final Cancer Policy will use quantitative risk assessments where data are available to develop a priority system for regulating chemical carcinogens. OSHA has determined that such risk assessments despite the range of uncertainty can provide a rough but useful guide for identifying overall health needs, along with other factors. Even at this level of analysis, OSHA recognizes that the large uncertainties inherent in the quantification of cancer risks require a priority system that is sufficiently flexible to accommodate the

qualitative information and policy judgments necessarily involved.

OSHA also believes that the benefits of a proposed regulation should be carefully examined where appropriate. However, where ranges of uncertainty are large, a single number "best estimate" (the most likely value) for risk is misleading. Rather a range of uncertainty must be recognized that constitutes crude guesses as to a probability distribution of risk. Traditional cost-benefit analyses undertaken in welfare economics do not encounter uncertainties of this magnitude. When great uncertainty as to risk exists the decision of what numerical value for risk accompanies a particular exposure level ceases to become objective in the rigorous scientific sense.

Further uncertainties for the validity of cost-benefit or cost-effectiveness computations enter in the predictions of compliance costs. Such analyses would require estimates of compliance costs at alternative levels of control. OSHA's considerable experience with cost projections for occupational health standards suggests that such estimates are very controversial, time-consuming and as the vinyl chloride case indicates, often highly inaccurate (see subsection #9 below). Such studies are generally forced to analyze the compliance costs associated with conventional techniques since the costs of untested technological and process innovation and changes in product characteristics cannot be easily determined.

Cost-effectiveness calculus would thus produce ratios of varying degrees of inaccuracy and comparability. In OSHA's view, the resulting estimates would produce numbers for comparison purposes that are highly speculative and carry great potential for misleading health determinations. A cost-benefit ratio is therefore an inappropriate decision rule for setting permissible exposure levels.

There are still other methodological difficulties undermining useful interpretation of cost-benefit results. The cost and benefit streams differ in temporal distributions. Determination of an appropriate discount rate for future benefits is controversial, yet the predicted benefits are highly sensitive to particular values selected. In addition, there are serious problems in valuing different kinds of benefits relative to each other (e.g., injury vs. death, pain, and suffering vs. loss of function). Many important social benefits never enter cost-benefit ratios since they are intangible and thus not easily converted to monetary dimensions.

For cost-benefit analyses of occupational health regulation, an especially serious methodological problem is involved where adverse health outcomes include premature death, because it would be necessary to assign a value to human life.

Attempts to assign economic weights to human life have often assumed a human capital approach, which values an individual's economic contribution to society. Human life valuation is calculated in terms of the present discounted value of future income streams (gross output) or the present discounted value of future income streams minus an individual's consumption (net output). This approach assumes that the only goal of economic policy is to maximize Gross National Product. Human life valuations also depend critically on earnings levels, leading to lower values for the retired, women, and disadvantaged low-wage groups (Ex. 220b–110,110D, 110N, 109 p. 57).

Another approach avoids any direct calculations of the loss of potential earnings or spending. Instead, the value of human life is implicitly calculated based on the cost of programs paid for by society that increase or decrease the number of deaths, such as the kidney dialysis program. However, estimates based on these "social" values have been found to differ widely depending on the program (Ex. 220b–110g).

Another methodology is based on insurance policies. Insurance premiums and death probabilities associated with specific activities have been used to calculate the value that individuals set on their lives. However, this approach is conceptually deficient since life insurance refers only to compensation to others.

Finally, attempts to value life have been based on estimates of wage premiums paid for high-risk occupations, using regression analysis. This methodology is based on the principle that workers in high hazard jobs will demand premiums to compensate them for the additional risks entailed. The annual (hourly wage) premiums required to assume the additional risks are then converted into estimates of the value of human life. The results of this methodology are mixed. Estimates of the value of human life (where risk premiums have been found) vary widely with average figures ranging between $100,000 and $1 million. In addition to technical analytical problems involved in individual studies, the general validity of this methodology rests on the assumption of perfectly competitive labor markets. Hence, this approach requires that workers possess accurate knowledge of risks and make well-informed choices, an unlikely assumption for workplace carcinogens, and that workers can readily move to lower-risk jobs.

Dr. Lave, an advocate of cost-benefit analysis, pointed out the difficulties of placing a value on life. He stated:

> "While dollars are the natural metric of abatement costs, they are alien to the measurement of benefits. As explained above, the notion of explicitly valuing premature death or morbidity in dollars is repugnant. (Shelling, 1968; Burger, 1976; Lave and Sesken, 1977). Nonetheless, the refusal do so can be shown to result in grave misallocation of resources and in capricious behavior." (Ex. 117, p. 13)

After examining all the evidence in the coke oven proceeding (made part of this Record in Ex. 220b), where extensive data and arguments were presented on whether it was appropriate to attempt to put a dollar value on life, OSHA concluded:

> "that these methodologies do not adequately quantify the value of life. Accordingly we decline so." (41 FR 48751)

The evidence presented in the Cancer Policy confirms this conclusion. OSHA believes that it is not possible for it to place a value on life and regulate on this basis.

Still another methodological problem occurs for cost-benefit analysis when comparing different technologies. A benefit-to-cost ratio, expressed as "lives saved (or cancers prevented) per dollar expended" is the criterion generally used for cost-effectiveness determination, but its use is frequently difficult when comparing alternative control technologies which control hazards with differing *reliability* and *comprehensiveness of protection.* (This was discussed at length in the economic section on respirators.)

All of these factors assure that cost-effectiveness or cost-benefit calculus would produce ratios of differing degrees of inaccuracy and comparability. In OSHA's view, the resulting estimates would produce numbers that are highly speculative. Methodological deficiencies make difficult technically correct, non-arbitrary comparisions of cost and benefits and render cost-benefit analysis inappropriate as the decision rule for setting permissible exposure levels for carcinogens.

Finally, Wilson's recommendation moved beyond cost-benefit analysis in attempting to establish the overall parameters for determining acceptable levels of occupational risks. Under comparative risk analysis, the risks of other voluntary and involuntary risks

that people live with are computed and these are used to establish boundaries for setting occupational exposure levels.

Various parties discussed the concepts behind Dr. Wilson's methodology for determining "acceptable" risk based on historically observed levels of voluntary or involuntary risks. Dr. Lave (above and Ex. 117) discussed at length various research attempts to analyze the risks that humans are willing to accept. He pointed out the conceptual and practical difficulties inherent in evaluations of risk, including the large variations in the risks that humans view as acceptable, the difficulties that individuals face in assessing risks, and the characteristics of risk that influence individual preferences for risk. These include whether the risk is voluntary or imposed, familiar or unknown, of immediate occurrence or indeterminate in the future, and whether the risk affects large number of people with low probability or small numbers with high probability (pp. 17–19).

OSHA does not find this approach convincing. The validity of this methodology for determining acceptable levels of occupational risk based on observed risk decisions in other areas hinges on several critical assumptions which are highly controversial. These include the individual's ability to properly assess risk; that past behavior is indicative of present attitudes; that existing levels of risks are acceptable norms; and the ability to define predictable patterns of risk tolerance. In OSHA's view, many of these assumptions appear inappropriate.

In addition, Dr. Lave noted that for some categories of risk, such as occupational risk, individuals demand greater reductions in risk levels than for other classes with larger objective risk probabilities. Lave attributed this to irrational behavior. OSHA draws a different conclusion. The risk-benefit evidence suggests to OSHA that there are complex non-additive dimensions to risk that invalidate simple comparisons between non-occupational voluntarily accepted risks and occupational risks (i.e., between familiar routine risks and the unfamiliar risks of workplace exposure to toxic substances).

In addition to the methodological problems outlined above, OSHA believes that as a matter of policy, efficiency criteria alone are not appropriate because they ignore equity considerations. The economic savings from less protective regulation accrue to industry in the form of higher profits and to consumers in the form of lower prices. But the costs are borne by workers through increased industrial illness and death rates.

Efficiency analysis cannot accommodate the distributional implications involved when the costs and benefits accrue to different subgroups. Welfare comparison could only be made if there is an acceptable method for aggregating individual utilities (satisfactions) into a social welfare function ranking alternative efficient arrangements in order of their social desirability. Unfortunately, it has been conclusively demonstrated that no satisfactory aggregation procedure is possible. As a result, economic analysis ignores equity considerations because they involve interpersonal comparisons of utility, whereby one group is made better off, while another is made worse off.

Dr. Ashford (MIT), discussed the implications of equity for cost-benefit analysis. He stated:

"The most serious limitation (of cost-benefit analysis), however, lies in the failure to successfully deal with the fact that the cost and benefit streams accrue to different parties. One person's benefit cannot be neatly traded off from another's cost. Maximizing social welfare should not necessarily be equated with optimizing social welfare. Equity and economic efficiency are sometimes conflicting goals. As a decision tool, cost-benefit analysis can be useful in identifying the nature of the trade-offs; as a decision rule it is useless. Regulation of toxic substances is an expression of social policy, not economic policy, and the social decision does not end with internalizing the social costs of producing and using chemicals and followed by equating costs and benefits at the margin." (Tr. 2402–3)

See also Dr. Ashford's discussion at pp. 2400–2402 and Dr. Hazleton's in Ex. 247, pp. III–1 to 3.

OSHA believes that it would be inappropriate for an agency statutorily required "to assure so far as possible every working man and woman in the nation safe and healthful working conditions" to ignore such equity considerations.

Finally, OSHA believes that the Cancer Policy approach to regulating carcinogens to the lowest feasible level most accurately reflects the requirements of the OSH Act because a safe threshold level of exposure cannot be demonstrated for carcinogens. This position has just been clearly stated by the D.C. Circuit in *AFL–CIO* v. *Marshall* (78–1562' 1/24/79), a decision upholding the OSHA cotton dust standard. The Court stated:

"Industry petitioners would have the court impose an additional constraint on OSHA's authority to determine standards. They claim that under the feasibility requirement, OSHA must demonstrate that 'the benefits of the standard are in proportion with the costs which it imposes.' This amounts to a claim that no standard may be promulgated under section 6(b)(5) of the Act absent a formal cost-benefit analysis. The industry similarly argues that OSHA must justify the expense imposed by its standard by comparing it with the industry's proposed alternatives.

"OSHA agrees that a systematic evaluation of costs and benefits is to be encouraged within the limits of available estimation techniques, yet it contends that such analysis is not requried. OSHA argues that the OSH Act constrains its regulation of dangerous substances 'only by the limits of feasibility.' We agree.

"We also find that no additional constraint is imposed by the Act's definition of a health or safety standard as reasonably necessary or appropriate to provide safe or healthful employment. The language of the Act and the clear intention of Congress permit no other conclusion.

* * * * * *

"In the OSH Act, Congress itself struck the balance between costs and benefits in the mandate to the agency. Section 6(b)(5) unequivocally mandates OSHA to set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity."

Thus Congress concluded that the benefits of health protection warranted the expenses of an effective standard.

. . . Congress determined in the OSH Act that any severe risk to employee health must be eliminated or reduced if feasible means to do so exist. This calls for a two-step analysis by the agency: (1) determining whether health impairment is threatened by the suspect substance, and (2) determining whether the selected strategy protect workers from this risk is both technologically and economically feasible. Nothing in the statute or its legislative history requires a further determination that the costs of the standard bear a "reasonable" relationship to its benefits.

"Further, cost-benefit analysis would not necessarily improve agency health and safety determinations. These techniques require the expression of costs, benefits and performance in often arbitrary, measurable terms. They may hide assumptions and qualifications in the seeming objectivity of numerical estimates. Especially where a policy aims to protect the health and lives of thousands of people, the difficulties in comparing widely dispersed benefits with more concentrated and calculable costs may overwhelm the advantages of such analysis.

OSHA considered the alternative proposed by the industry and found it inadequate to protect against the health risk at issue. We recognize that the agency's control strategy is costly. But it is the result of long and comprehensive investigation by the agency assisted by extensive public participation. (Slip opinion pp. 51–52.)

OSHA's choice of the lowest feasible level has also been approved in *Industrial Union Dept.* v. *Hodgson*, 499 F. 2d 467 (D.C. Cir., 1974), *American Iron*

and Steel Institute v. *OSHA*, 577 F. 2d 825 (3rd Cir., 1978) and the *Society of Plastics Industries* v. *OSHA*, 509 F. 2d 1301 (2nd Cir., 1976). This approach has been rejected in *American Petroleum Institute* v. *OSHA*, 581 F. 2d 4931 (5th Cir., 1978), cert, granted. The Agency has appealed the Fifth Circuit's decision on the basis that the Act and Congressional intent require that employee exposure to carcinogens be reduced to the lowest level feasible.

To summarize, in examining the Record on the generic cancer policy it is clear that the same criticisms of the Secretary's decision-making process are raised which were raised in previous hearings on specific standards. The criticisms fall into three areas: (1) specific disagreements concerning health, technological or economic data, (2) the depth of analysis taken in risk assessment or technology/economic evaluations and (3) the Secretary's decision rule regarding the extent and nature of worker protection required by employers.

The first type of criticism is discussed in other sections of the document. The second type has been explained at great length in this section. The Secretary has always recognized the importance of undertaking risk and technology/economic assessments. However, the depth of such analyses should not be pushed further than the state-of-the-art justifies. The difficulties involved in performing risk assessments, especially for carcinogens, have been enumerated both in this section and in Section VIII. Unlike classic toxic substances, there are no demonstrated safe levels of exposure for carcinogens. Risk estimates for carcinogens involve a wide range of uncertainty. For carcinogens, a single point-estimate of risk may understate or overstate actual cancer risks by orders of magnitude. The actual risk may be factors of 10–10,000 larger or smaller. A single number "best estimate" for risk is therefore not appropriate. Rather, a range of uncertainty must be recognized which constitutes crude guesses as to a probability distribution of risk. Traditional cost-benefit analyses undertaken in welfare economics do not encounter uncertainties of this magnitude. When great uncertainty as to risk exists the decision of what risk accompanies a particular exposure level ceases to become objective in the rigorous scientific sense.

In choosing among alternative strategies to control hazards, more than the costs of control must be taken into account. Technology assessments must include an evaluation of both the technical reliability and comprehensiveness of protection of alternative technological approaches.

A benefit-to-cost ratio, expressed as "lives saved (or cancers prevented) per dollar expended" is the criterion used for cost-effectiveness determination in traditional cost-benefit analyses, but its use is methodologically inappropriate in the control of carcinogens. Traditional cost-benefit criteria are inappropriate decision rules for setting exposure levels, where estimates are highly uncertain and where economic evaluations of alternative control technologies involve wide-ranging differences in reliability and comprehensiveness of protection. In addition, traditional cost-benefit analysis takes no cognizance of equity considerations which are paramount to occupational health regulation.

The Secretary concludes, for all the reasons discussed above, that while a careful examination of the costs and benefits of a proposed regulation may be useful, a cost-benefit decision rule is an inappropriate basis for setting permissible exposure levels of worker exposure to carcinogens.

Relevant to the third criticism, the Secretary's mandate under the OSH Act is clear and specific as to the degree of protection required to be provided to workers from exposure to toxic substances. As long as there are workers faced with a risk of "material impairment", protection must be provided "to the extent feasible." Discretion as to what constitutes material impairment or what is feasible lies with the Secretary and has been shaped by the court decisions. Cancer is an irreversible disease leading to death with no threshold or safe level and thus requires a highly protective approach. In addition, this approach has been successful in protecting employees in the past, has not created significant economic disruption in prior regulations and is consistent with the requirements of the Act.

In conclusion, this process reflects not only the clear legislative mandate discussed above, but also avoids methodological problems which make alternative decision rules inappropriate. Therefore, the final Cancer Policy retains the proposal's provision that worker exposure to confirmed carcinogens is to be reduced to the lowest feasible level taking into account technological and economic considerations.

(8) General Amendments to the Part

The OSHA Cancer Policy establishes procedures for regulating industrial carcinogens designed to streamline the promulgation of standards for hazardous substances. Numerous public comments were received on the advantages of a generic approach to regulating carcinogens. Such a policy would increase the efficiency and consistency of OSHA's rulemaking on carcinogens by resolving certain issues that are routinely raised in individual proceedings based on widely accepted scientific principles and prudent policy judgments. Adopting these principles as a matter of policy will permit more timely issuance of regulations and more effectively utilize agency resources. A more systematic and predictable approach to regulating carcinogens will also provide industry and workers with improved information on future regulatory actions.

A generic policy will thus assure that subsequent regulations achieve a greater overall reduction in the incidence of workplace cancer. (Section II presents a more detailed discussion of the relative advantages of a generic approach to regulating chemical carcinogens).

Industry witnesses argued that by establishing a generic policy, OSHA would not be able to keep pace with the fast-changing science of cancer or technological advances. The principal economic issues centered on concern that OSHA determinations regarding primary control strategies and the role of risk assessments would nullify any future significant developments in respirators that might make them equally as effective as engineering controls or in risk quantification techniques.

OSHA has determined after careful review of the evidence that the current state-of-the-art requires primary reliance on engineering and work practice controls to effectively control exposures to potential occupational carcinogens and on achieving the lowest feasible level to assure maximum health protection. (See discussion above and in Section VD10).

However, the final OSHA Cancer Policy has expanded opportunities for amendment of the policy. The policy provides amendments based on procedures for individual petitions, recommendations of the federal health research institutes, and periodic agency review (at least every three years) to permit consideration of significant scientific and technical advances. (§ 1990.106). Such reviews will assure that any significant unanticipated developments in control technologies or risk methodologies that render current state-of-the-art practices obsolete are not precluded from future consideration. In addition § 1990.145 permits amending the policy in the course of a substance specific rulemaking if substantial new

evidence becomes available. Such procedures assure that technological breakthroughs in respirators or scientific advances in risk quantification techniques could be accommodated to the extent appropriate through suitable amendments to the Cancer Policy. The amendment procedures are analyzed in Section IX.D.

(9) The "Snell Report"

The Snell Report (S. III–104 R & S) submitted by the American Industrial Health Council attempted to assess the total cost impact of the carcinogen proposal. OSHA has carefully evaluated both the report and relevant public comments and concluded that the Snell estimates have little predictive value. This conclusion is based on both the particular methodology employed in the study and on conceptual and practical difficulties associated with applying such costing procedures to generic standards in general. OSHA believes that meaningful economic analyses can only be performed for individual regulated substances. The Cancer Policy provides for a careful analysis of exposure levels, costs, and feasibility including technical and economic considerations in the rulemaking proceeding for the regulation of each individual chemical.

The Snell study developed cost estimates for regulating 7 substances and a composite group of pesticides at alternative exposure levels. The case studies used confidential data submitted by producer and user industries. Total cost estimates of the Cancer Policy were extrapolated from this base. The survey data and additional evidence obtained from prior OSHA regulations and public sources were used to deduce estimating factors reflecting compliance costs of regulating the case-study group of chemicals at alternative control levels. These substance-specific cost factors were expressed in terms of a base unit (percent of value of shipments for producer industries and per exposed employee for user industries). Separate cost factors from different data sources were combined with the case study factors in some fashion to produce composite estimating factors for the specific substances. The factors used relied heavily on "study team" judgment rather than on more objective engineering or statistical criteria.

To obtain overall cost estimates for the Cancer Policy required specification of the future number of regulated chemicals and the stringency of permissible exposure limits for Category I Potential Carcinogens. The study developed several regulatory scenarios for these parameters. The number of regulated substances assumed ranged from 38 to 2,415 chemicals. The 2,415 substances include all chemicals on the NIOSH list where there has been any literature reference of possible carcinogenicity. Alternative permissible exposure levels selected were 10 ppm, 1 ppm, and below 1 ppm. Portions of these chemicals groups were designated as Category I or Category II Potential Carcinogens according to certain assumptions. Crude assumptions regarding multiple exposures, substitution possibilities, and technological developments were used to adjust overall coverage (value of shipments and exposed employees) categories for groups of chemicals.

The extrapolation technique used involved multiplying these adjusted values of shipment or exposed employee figures by the appropriate estimating factors, to produce total cost estimates under various regulatory scenarios. Based on this methodology, the study calculated estimates of capital costs ranging from $9 billion to $88 billion and annual costs from $6 to $36 billion depending on assumptions concerning the number of chemicals regulated and levels of engineering control.

A large number of criticisms directed at the Snell Report conclusions took issue with specific technical aspects of the study design, data base, and project implementation. These will be discussed in the following sections.

Numerous data inadequacies undermine the validity of the Snell analysis. The study attempted to project costs from a narrow base of 7 case studies and some additional data to a large universe of chemicals. Given the wide diversity in chemical properties, routes of entry, production processes, and time-weighted exposures, it is not clear whether these 7 substances can be considered representative of the potential chemical population. Snell made no attempts to validate whether these substances were appropriate as proxies for the total universe.

The small sample size and low response rate to the study survey (only 76 questionnaires of the 7,000 printed copies were received from 9 companies) could have introduced serious unkown biases in sample characteristics for substances, industries, exposure levels, processes and other relevant technical determinants of costs.

In addition to potential sample biases, the small size of the primary data base also reduces the statistical reliability of the projections. (In statistical terminology, as the sample size increases, the sample mean approaches the population mean; *Law of Large Numbers.)* Snell agreed in response to oral questions:

A. Dr. Nemec (Snell): "It is correctly stated that as we move further away from the seven case studies, the accuracy of the data base decreases." (Tr. 2850–1)

The importance of sample size for estimation accuracy is accentuated for the user industries which have substantially fewer survey observations but incur approximately 95 percent of the compliance costs. For example, Snell estimated for the medium scenario that producer industry capital costs would total $0.4–$1.1 billion or 2 percent of total capital costs. The other 98 percent ($16–$46 billion) of capital costs would accrue to the user industries. (St. III–104R p. IA–2.)

Witnesses also pointed out weaknesses in the data collection methods used by Snell. Data confidentiality provisions precluded assessment of the reliability of the data base (Tr. 3876–7). The opportunity for independent evaluation of the data set is important given the large variance in compliance costs among substances and within producer and consumer industries and the costing method's dependence on employer-based surveys. Dr. Hazleton, Associate Dean and Professor in the Lyndon B. Johnson School of Public Affairs at the University of Texas, an economic consultant to OSHA, brought out through his questioning (Tr. 3961–2) and also stated in his comments (Ex. 247, p. IV–13, n. 2) that had an appropriate methodology been followed the underlying data could have been made available while confidentiality was maintained.

Dr. Hazleton also criticized the questionnaire language for a design bias which would encourage employers to exaggerate cost impacts. For example, the questionnaire stated that "the proposed regulation would lead to a flurry of regulatory activity" and that an industry committee "believes that the OSHA proposal might result in the improper classification of a substantial number of substances and that the proposal's economic costs might be out of proportion to its possible benefits." (p. IV–11 to 12.)

Although Snell argued that the study employed an engineering approach to estimating costs, they conducted no engineering evaluations of specific control technology, environmental monitoring or analysis of exposure data, which are conventional techniques for engineering analysis. Instead, Snell relied heavily on data supplied by industry in the case studies and questionnaires. No independent

supportive evidence for evaluating the validity of the cost estimates were collected outside of a few plant visits and contacts with a few suppliers of control technology. (Tr. 3872–8)

The costing methodology primarily assumed that compliance would be achieved by conventional control technology and processes. Retrofit technology often proves to be an expensive control strategy relative to installation of new processes or technologies that are more cost-effective or efficient control strategies. Retrospective studies of the vinyl chloride industry showed that substantially lower compliance costs were achieved through innovative alterations in production processes. (See discussion below.)

Data base problems are further compounded by weaknesses in the techniques used to extrapolate the total cost impacts of the Cancer Policy. These methodological difficulties arise from several sources. First, the estimating factors critical to cost projections (see general discussion above on the Snell study methodology) were not derived in any consistent or explainable fashion. Estimating factors for chemicals were computed separately from the 7 case studies, economic studies prepared for other OSHA regulations, and other survey sources. These separate estimating factors were then combined in some manner to obtain overall estimating factors for individual chemicals. Snell did not take a mean or median figure or utilize some generally recognized engineering or statistical formula. Instead, the overall estimating factors relied heavily on "study team judgment." Snell stated in response to questions:

A. Dr. Nemec (Snell): I would call your attention to Appendix E–1–3 at the bottom of the page we indicate the average and standard deviation as well as the ultimate factor used which is labeled "Study Team Judgment." * * * (Tr. 3939–40)

In addition, differences in data accuracy would seem to dictate that estimating factors derived from the case studies be weighted most heavily. In fact, the overall estimating factors chosen are consistently higher than the mean or median of the estimating factors derived from the case studies. Dr. Hazelton stated,

"In the question period, it was pointed out that the study team judgment in many instances produced a figure which was considerably in excess of the mean or median observation for the case study substances. For example, for Category I substances at a PEL of 10 ppm, the study team judgment is 2.2 percent of the final value of shipments for capital costs in the substance producing industries. Note that as shown in Table 3B above, the mean of the case study observations was 1.4 and the median was 0.9. Recall also the Snell had previously reported that '* * * as we move further away from the seven case studies, the accuracy of the data base declines.' Nonetheless, in this case, as in many others, Snell's judgment appears to have ignored the case study data and to have selected a number which is more representative of additional inputs, in this case selecting 2.2 which is just below the median of the additional inputs. In neither the Snell Study nor the Snell Testimony, does one find any discussion of how these judgments were reached, other than the comment that they represented the collective wisdom of a team of experts." (Ex. 247, IV–25–26; See also Tr. pp. 3954–61).

For the user industries in particular, the average cost factors derived from the case studies are consistently much lower than the aggregate cost factor used. No reason for selecting the cost factors used are supplied despite the fact that the user industry exhibits a greater range of potential cost factor values and user industry estimates dominate the total estimated costs of the proposal. The manner in which these estimating factors were modified to determine ranges of estimates are also not explainable in any consistent fashion.

Witnesses also criticized the value of shipment and number of employee bases. Dr. Hazelton points out that no particular justification is given on the appropriateness of utilizing the value of final shipments and numbers of employees exposed as the base unit for the estimating factors. Possible alternatives, for example, would be pounds of chemicals shipped, or number of workplaces with exposures. Further, because Snell did not supply underlying data, there is no way of analyzing the base choice selected. (Ex. 247, pp. IV–14–15).

These bases were adjusted to reflect alternative regulatory scenarios on the number of chemicals regulated and stringency of control requirements. (See discussion above on general methodology of the Snell Report). Many witnesses criticized the crude assumptions used to develop these scenarios. Particular criticism was directed at assumptions for the number of chemicals regulated, the classification of substances as Category I or II Potential Carcinogens, the 1.5 estimate of multiple exposures, the standardized cost estimates for nonengineering controls in user industries, and various control requirements (e.g., at 10 ppm, 50 percent of employees in user industries would require engineering controls). The particular assumptions used often appeared arbitrary and without much supporting documentation. Some provided unrealistic scenarios of likely regulatory options under the Cancer Policy.

These methodological problems led many witnesses to conclude that the Snell Study estimates could not be interpreted in any meaningful way. The Report of the Regulatory Analysis Review Group submitted by the Council on Wage and Price Stability concluded that "there are a number of major methodological problems with the BAH (Booze Allen & Hamilton or Snell) study which makes it impossible to place great confidence in its results." (Ex. 253, p. 12. Appendix A of the Report analyzes those problems at length.)

Dr. Hazelton came to similar conclusions. he stated:

"Given the reliance on confidential data which was not included in the report, and which was elicited in a manner which would tend to bias upward the estimates; the extreme variation in compliance cost estimates among substances for both the substance producing and using industries; the doubtful basis of the selection of the three scenarios; and the frequent reliance on judgments that are not explained, it is not possible to come to any conclusion about the validity of the Snell compliance cost estimates other than that it would be a mistake to place any reliance on them." (IV–26–27).

Snell submitted two responses to the criticisms dated September 11, 1978 (Ex. 218) and October 23, 1978 (Ex. 251C). Snell argued that its critics misinterpreted the scope and objectives of the report and failed to take into account the limited time available for its preparation. Technical responses were made regarding the choice of estimating factors and the handling of multiple exposures. In its Post Hearing Brief (Ex. 251A), the AIHC industry group stated that the "AIHC does not argue that the Snell estimates are hard numbers upon which regulatory decisions should be made, but rather that they are indicators of the need to take a closer look." (pp. 110–111).

OSHA has carefully reviewed the Snell study and various criticisms of the analysis. This preamble has detailed OSHA's assessment of various technical issues. Based on that review, OSHA agrees with the conclusion of a number of participants that the Snell estimates are unreliable and hold little predictive value as indicators of the likely cumulative cost impact of all future OSHA regulations of carcinogens.

Certain parties to the rulemaking recommended that OSHA perform a more comprehensive economic analysis. (See, for example, the Regulatory Analysis Review Group (Ex. 253) and

the AIHC (Ex. 251A)). The agency has declined to do so for three reasons.

First, the Cancer Policy, which is designed to structure and speed-up the regulation of cancer-causing chemicals will not directly impose economic burdens.

Second, while the Cancer Policy will "affect" costs of individual standards (e.g. by requiring primary reliance on engineering controls for Category I Potential Carcinogens), it incorporates the requirement that standards be feasible. Specific determinations of feasibility will be made in the context of individual rulemaking proceedings.

Third, on the basis of careful evaluation of the Snell methodology and alternative techniques, OSHA has determined that it is not possible to estimate meaningful costs for the cancer policy for several reasons.

Both the Snell study and economic studies performed by OSHA for individual substances indicate that cost of compliance estimates for the Cancer Policy and for health standards in general are highly sensitive to the specific values selected for parameters which cannot be reasonably determined at the present time and which can only be resolved during rulemaking proceedings for specific chemicals. These variables include: the number of chemicals regulated, particular chemicals which prove to be carcinogenic, category of regulation, exposure levels established, control strategies, presence of action level or percentage exclusion provisions (see discussion above) and compliance periods.

For example, the incremental annualized costs of compliance for a new acrylonitrile standard varied over 110 percent, from $24 million to $84 million depending on the permissible exposure limit selected. Annualized costs of compliance for the cotton dust standard also varied significantly (by over 175 percent) depending on differences in levels of control. For the Snell study, estimates of the total direct costs of the cancer proposal differed by over 600 percent depending on the number of substances or stringency of control assumed. Snell accepted this point.

Q. "So that in fact there could be a very, very large variation in the estimate, depending upon how all these seven categories were handled."

A. Dr. Nemec (Snell): "Indeed." (Tr. 3868).

Retrospective analysis of the vinyl chloride study performed for OSHA by the same Snell Division illustrates the difficulties involved in projecting reasonably accurate costs to achieve compliance of just one chemical, to a specified control level, in an industry with relatively few plants and similar processes. The Snell vinyl chloride report predicted that the lowest feasible levels which could be achieved for the VCM industry was 2–5 ppm at an estimated direct capital cost of $24 million (Tr. 3896, Ex. 68, Chart (Exhibit) V–4). It estimated that the lowest feasible level achievable in the PVC industry was 10–15 ppm at a direct capital cost of $140 million (Tr. 3896–7, Ex. 68, Chart (Exhibit) V–9). Total costs for the VCM and PVC industries were at these levels estimated at $164 million. Snell also derived a cost estimate for attempting to achieve 1 ppm, which they argued would not be feasible. The estimated $564 million in direct capital costs for the VCM industry to attempt to achieve 1 ppm (Tr. 3898–9; Ex. 69, Chart (Exhibit) V–10). They estimated costs for the PVC industry to attempt to achieve 1 ppm at $1.35 billion (Tr. 3900–3; Ex. 65 Exhibit V–14). In fact, both industries did achieve the 1 ppm level in about three years at a cost of $22 million for the VCM industry (Tr. 3889). The $2 million figure in the transcript should be $22 million—See S. 104 R, pp. VA 14 and 22) and at a cost of $105 million for the PVC industry (Tr. 3889). Therefore, actual cost figures for achieving the 1 ppm control levels selected by OSHA are only about 7 percent of predicted costs, $127 million versus $1.91 billion. In fact, the actual costs to achieve the 1 ppm level were less than the estimates derived by Snell to achieve 2–5 ppm for VCM and 10–15 ppm for PVC.

Snell disputes that their "no detectable level" estimate in the 1974 prospective study was for the 1 ppm level, claiming that the "no detectable level" that they costed out was below 1 ppm. However, at the time of the study, it appeared that 1 ppm and "no detectable" level were in fact similar. The scientific evidence on the state-of-the-art regarding measurements using available sampling techniques was mixed. Some experts indicated that 1 ppm was the lowest readily detectable level then in the factory setting while other experts pointed out that lower levels were measurable in the laboratory setting. The Snell vinyl chloride report uses different formulations in several places. The study conclusions, however, suggest that 1 ppm approximates the "no detectable" level. It states:

> "Based on the industry survey and Snell's independent assessments of the state-of-the-art of the technology, it is concluded that achieving 'no detectable' (0–1 ppm) VCM levels in the VCM industry is not feasible principally through engineering means." (Ex. 68, p. VI–1, the same statement is repeated on that page for the PVC industry.)

The evidence and discussion above clearly indicates that it is not possible to estimate with any validity the future costs of regulating a currently unknown number of chemicals to unspecified levels of control.

These uncertainties are further compounded in the final Cancer Policy which establishes a priority system and more flexible, "cost-effective" model standards provisions. The OSHA priority system influences the timing of regulations. The Snell methodology assumed a simple comparative static framework whereby *all* substances for regulation as defined under the various scenarios were assumed to be simultaneously and immediately regulated. While problems exist with this methodology, it could be justified as a reasonable simplifying assumption based on the automatic regulatory requirements triggered by classification of a substance as a Category I or II Potential Carcinogen and the provisions for issuance of final regulations within prescribed timeframes. The fixed baseline established by this methodology can be readily compared with one of "no regulation."

The final Cancer Policy's inclusion of a priority scheme that eliminates automatic regulatory triggers invalidates this simple approach. With a priority system, different baselines for substances would be required to reflect the order and timing of standards issuance. Such baselines simply cannot be reasonably forecast. They would require knowledge of a series of complicated and unknowable issues such as the relative priority for regulation of all currently known and unrecognized serious occupational health hazards, the intertemporal distribution of capital costs, technology life-cycles (both plants and equipment) and future opportunities for technological innovation. The final standard also improves the flexibility and cost-effectiveness of standard provisions, introducting yet more uncertain dimensions into a cost analysis.

Thus, OSHA believes that the total cost impact of future standards issued pursuant to OSHA's Cancer Policy cannot be estimated because of the enormous uncertainties surrounding the set of specific chemical substances (many of which are presently unknown), the exposure level set after feasibility analyses, standards provisions to be established, and the order and timing of future substance-by-substance regulation. There are simply too many

unknown variables that preclude development of a meaningful system for estimating the cumulative costs of the OSHA Cancer Policy.

These complexities could be even further expanded if OSHA were to attempt to estimate the marginal cost of OSHA's generic approach to regulating carcinogens versus other possible approaches. Since occupational carcinogens would continue to be regulated in the absence of the Cancer Policy, OSHA believes that estimation of incremental costs is conceptually the proper methodology.

Dr. Hazleton, after an extensive analysis of the Snell report for the AIHC, drew similar conclusions:

"The estimates of direct compliance costs developed by Snell cannot be attributed to generic regulation *per se*, but rather must be viewed as estimates of compliance costs which result from the regulation of occupational carcinogens—whether this regulation occurs under the provisions of OSHA's proposed generic approach or under other procedures. Thus, the Snell cost estimates are not *incremental costs*. In the absence of generic regulatory procedures, it must be assumed that the occupational health objectives mandated by Congress would continue to be addressed by OSHA through a case-by-case approach.

". . . However, it should be recognized that it is highly unusual to attempt, and extremely difficult in practice to determine the prospective costs of a proposed *policy*, such as is represented by the generic rulemaking, as opposed to specific, proposed *programs*." (Ex. 247, pp. IV–7 to 8)

This incremental methodology would replace the "no regulation" baseline with various scenarios reflecting what OSHA would have done in the absence of a generic regulation. This would be compared with scenarios regarding the future regulatory programs. Although this approach would be conceptually more appropriate than the Snell approach, it would be even more difficult to carry out in a defensible manner. There would be an additional set of essentially unpredictable variables to factor into the analysis. OSHA therefore agrees with Dr. Hazleton's conclusion that such an analysis would be "highly unusual to attempt and extremely difficult in practice to determine."

The serious conceptual difficulties described above confirm OSHA's conclusion that conventional economic analyses would be more usefully performed in the context of individual substance rulemakings. The OSHA Cancer Policy, which is designed to structure and speed-up the regulation of cancer-causing substances, will not directly impose cost burdens. To the extent that it will affect the costs which will be created by individual standards it requires that these costs be feasible for affected industries. The proper approach for analysis of the Cancer Policy involves a discussion of possible policy approaches that could be used in generic regulation. OSHA placed in the Record a Regulatory Analysis of the Cancer Policy on October 24, 1978 which discussed alternative policy approaches and examined several possible classification schemes and parameters used to determine feasibility. The Preamble discusses in detail various alternative approaches for specific issues.

Under the Cancer Policy, OSHA will perform economic studies for individual regulations. Such specific cost analyses will have a better chance of being reasonably accurate, and are directly relevant to the industries and workers being regulated for development of an appropriate regulation, consistent with OSHA's statutory mandate. OSHA believes that such analyses will improve the effectiveness of regulations by assuring that all available and relevant technical, economic and health information will be taken into consideration in the regulatory process.

C. ENVIRONMENTAL CONSIDERATIONS

The OSHA proposal included a Draft Environmental Impact Statement (Ex. 1, 42 FR 54180, et seq.). The draft pointed out that any environmental impact of the OSHA Cancer Policy was primarily limited to the internal or workplace environment. It pointed out that the majority of the proposal's preamble discussed those impacts at length and they were favorable, resulting in a reduction in occupational cancer. The draft incorporated by reference that discussion of the workplace environment.

The Draft Environmental Impact Statement (Draft or DEIS) pointed out that the Cancer Policy did not specify the particular chemicals which were to be regulated. Possible impacts on the external environment, if any, would by and large be dependent on the characteristics of the particular chemicals to be regulated. The Draft further pointed out that because chemicals to be regulated were not specified, attempts to quantify external environmental impacts would be speculative and therefore perhaps not appropriate or required before specific chemicals were proposed for regulation. The Draft noted that investigation of external environmental effects of specific chemicals would be appropriately done at the time a regulation of a chemical was proposed where facts would be available. The proposed Cancer Policy provided that environmental issues, including, of course, the requirements of the National Environmental Policy Act were to be considered during the regulation of individual chemicals.

The Draft did discuss the external environmental effects of some general regulatory provisions. It pointed out that certain types of engineering controls which sealed the carcinogen within the process, tended to improve the external environment by reducing the carcinogen's escape both into the workplace and external environment. However, other types of engineering controls such as ventilation would not improve the external environment (unless, of course, filters of various types were installed). The Draft also discussed the external environmental effects of various control levels and regulations of differing scope.

The Draft requested comments and information on all environmental issues. The proposal also indicated that all possible environmental consequences of the proposed Cancer Policy were an issue in the proceeding and requested comments and data.

OSHA reviewed 52 comments in direct response to the Draft. However, 45 either made no specific comments or stated generally they approved of the Cancer Policy proposal. Only three of the comments referred to traditional environmental concerns (air quality, water quality, waste disposal, etc.) and none presented specific factual information. (The other comments mentioned scientific issues discussed elsewhere in the preamble). However, OSHA received a number of criticisms for not engaging in a more extensive investigation of possible external environmental effect of the Cancer Policy and possible alternatives. (See for example, NRDC, C. II–270, pp. 54–56 and AIHC, Ex. 251A, pp. 82–95)

OSHA decided to undertake a more comprehensive investigation of possible external environmental impacts of its prior carcinogen regulations, the proposed Cancer Policy and various alternatives. The results of that investigation are included in the Final Environmental Impact Statement (FEIS or Final) which has been published. (Copies are available from OSHA's Office of Regulatory Analysis, Rm. N3651 200 Constitution N.W., Washington, D.C. 20210, Tele. (202) 523–7056.)

The following discussion summarizes the FEIS. In large part, the FEIS confirms the conclusions drawn in the Draft; however, certain changes in the final Cancer Policy have been made to make

it more sensitive to environmental concerns. Discussion of the effect the final Cancer Policy and the alternatives will have on the internal or workplace environment are, of course, discussed in other parts of this preamble.

In preparation of the FEIS, OSHA reviewed the external environmental effects of four prior OSHA carcinogen regulations, vinyl chloride, coke oven emissions, benzene and arsenic. A major source of information was EPA studies of the effects those regulations had on the external environment. The EPA studies include, in some cases, engineering studies, computer models, and, in the coke oven case, measurements of the reduction in external emissions from controls installed to meet the OSHA standard.

The results of the study are explained at length in Chapter VI of the FEIS. For example, controls required by OSHA reduced charging emissions from coke ovens by 88% and door leaks by 65% into the external environment. Solvent cleaning installed to meet the OSHA vinyl chloride regulation reduced the need to open the reactor from every batch to once every 80 batches. This reduced vinyl chloride emissions into the external atmosphere from 0.14 to 0.0018 Kg vinyl chloride monomer (the carcinogen) for every 100 Kg of polyvinyl chloride (PVC) produced.

The conclusion of the FEIS is that the four prior OSHA carcinogen regulations had already or would improve the external air quality. The reason for this is that certain types of engineering and work practice controls which enclose the carcinogen within the process equipment, prevent the carcinogen from escaping into the external atmosphere as well as into the workplace environment. Ventilation controls with filters, baghouses or electrostatic precipitators also may benefit the external environment, but they will not, if the ventilation controls do not have filters. Other types of engineering controls such as clean rooms and pulpits, and respiratory protection will not have effects positive or negative on the external environment.

Both the proposed and final Cancer Policy put primary emphasis on the use of engineering controls as the control strategy. The FEIS indicates that this approach is preferable for environmental resources as well as for the other reasons it has been chosen, which are discussed in Sections X–7 and XI of this document.

Since individual regulations issued pursuant to the Cancer Policy will be similar to the four analyzed prior regulations in the emphasis on engineering controls, and in other relevant respects, it is a reasonable prediction that regulation issued under the Cancer Policy will also benefit air quality. This, of course, may not be true in every case. But the environmental impact assessment or statement, which will be carried out for individual regulations, is the appropriate method for identifying exceptions and indicating responses to eliminate problems.

It also is a reasonable generalization that the future OSHA carcinogenic regulations under the Cancer Policy will not have significant effects on water quality or waste disposal as past regulations have not. But exceptions will be appropriately investigated and ameliorative strategies identified during the regulation of specific substances, as provided for by the Cancer Policy.

The FEIS also confirmed the analysis of the Draft that the main focus of environmental investigation must be at the time regulation of specific chemicals is proposed. The FEIS points out that chemicals have different properities and possible external impact are heavily dependent on these particular characteristics. The environmental impacts of regulating gases, liquids and particulates, and chemicals with different toxicities and uses will be different. For example, arsenic is used as a wood perservative. Wood perservatives by extending the life of wood reduce the demands on forest resources and reduce the need to use persistent pesticides. The arsenic FEIS investigated and determined that there would be adequate suppliers of arsenic for this purpose. However, this particular impact is, of course, substance specific to arsenic and could only be determined in an environmental impact statement for a particular chemical.

The FEIS points out that even similar controls for similar processes may have different environmental effects. Copper smelting and coke oven production are both large scale, high temperature operations involving large furnaces. Negative pressure (as a control) while charging coke ovens is environmentally sound. However, negative pressure to reduce arsenic emissions from reverbatory furnaces during copper smelting, may result in increasing sulfur dioxide emissions to the external atmosphere.

Examples like these further indicate that the main thrust of environmental investigation should be at the time that regulation of a specific chemical is proposed. Both the proposed and final Cancer Policy provide that environmental issues are to be considered during the regulation of particular substances.

The Final Environmental Impact Statement examines the possible differential external environmental effects of the proposal and 7 alternatives. The alternatives were the proposals suggested by AIHC, API, DuPont, NRDC and AFL–CIO–USW. It also included an analysis of an "integrated" alternative, which is very similar to the final Cancer Policy and a "no action" alternative. The FEIS identifies nine areas of possible differential external environmental effects. These were speed of regulation, predictability, priorities, control level, control methodologies, suitable substitutes action levels, percentage exclusions and model standards. It then examines the possible differential external environmental effects of the proposal and the 7 alternatives in each of the areas. The following discussion briefly summarizes the FEIS findings in each area and OSHA's response in the final Cancer Policy.

The FEIS analysis indicated that the proposal, NRDC, AFL–CIO and integrated alternative would result in quicker regulation than the DuPont AIHC, or API alternatives. The DuPont and AIHC alternative provide for an additional stage, the scientific panel, which would slow the regulatory process as would the API's lack of clear classification scheme. Regulation of occupational carcinogens is likely to benefit the external environmental as well as the work place environment, as discussed above. Therefore the final Cancer Policy and those alternatives which are likely to lead to a quicker regulatory response are likely to be more beneficial to the external environment overall.

The FEIS indicates that more predictable regulation is likely to increase voluntary control actions before regulation is completed and that this may benefit the external environment. The proposal and all the alternatives except the API and "no action" alternative are likely to be advantageous in this respect. Their relatively concrete classification schemes will improve the predictability of regulatory response. Of course, the final Cancer Policy also has a specific classification framework.

The Final Environmental Impact Statement analysis indicates that a priorities system, which the alternatives had, but which was not included in the proposal, would benefit the external environment. The final Cancer Policy, as discussed in Sections IX-G and XI of the preamble, includes a priorities system. There are many reasons for the inclusion of a priorities system in the

final Cancer Policy, including its beneficial environmental effects.

The final Cancer Policy has also specifically incorporated external environmental effects as one of the factors to be considered in setting priorities for the regulation of occupational carcinogenesis. See § 1990.132(b)(4).

Lower exposure levels may be more beneficial to the external air quality if, they are achieved through engineering controls. The FEIS indicated that those controls which will tend to result in lower workplace exposures will tend to reduce external emissions more. (There may be possible exceptions which must be determined for each substance.) The final Cancer Policy and those alternatives which set the lowest feasible exposure level may therefore have advantages in this respect over the alternatives which set an exposure level based on cost-benefit analysis.

As discussed above, certain types of engineering controls will provide significant benefits to the external environment. The final Cancer Policy, the proposal, the NRDC, and the AFL–CIO–USW alternatives place a greater emphasis on engineering controls than the other alternative, though all alternatives suggest that there should be a reference for engineering controls.

The final Cancer Policy provides that environmental issues are to be considered in the regulation of specific carcinogens. The FEIS indicates that some types of engineering controls have greater benefits to the external environmental than others. This is one of the issues which may be considered in a substance specific rulemaking as an environmental issue.

The FEIS indicates that in some circumstances substitution will benefit the external environment and in other situations it will not depending on the qualities of the substitute. This issue is appropriately considered in the context of the regulation of a specific chemical where substitution in proposed, as is permitted by the final Cancer Policy.

Most of the alternatives recommended the inclusion of action levels and percentage exclusions, lower level cut-offs below which most or all of the provision of a standard do not apply. The proposal did not include either of the concepts. The analysis in the FEIS indicated that in some circumstances action levels (and percentage of exclusions) may benefit the external environment and in other circumstances they do not.

One example discussed in the FEIS where an action level benefited the external environment is in the case of vinyl chloride. The standard provided that if exposures were kept below one-half the permissible exposure level, then the provisions of the regulation did not apply. As a result manufacturers of PVC developed better stripping techniques to reduce the residual carcinogenic monomer from the PVC plastic. In consequence, fabricators of the plastic could keep exposures of their workers below the action level and there was less residual monomer to escape into the external atmosphere.

OSHA has in the final Cancer Policy made it an issue whether an action level or percentage exclusions should be included in the regulation of individual substances. At that time, environmental considerations will be one factor which may be taken into account in determining whether the inclusion of an action level or percentage exclusion is appropriate.

The FEIS points out that in some circumstances provisions of the model standard will have no effects on the external environment and in other circumstances they may improve it. This needs to be considered in the context of a proposed regulation of a specific chemical.

In conclusion, OSHA has prepared a Final Environmental Impact Statement. Environmental considerations have been taken into account in the preparation of the Cancer Policy and will be taken into account in the issuance of individual standards pursuant to the Cancer Policy.

XII. OTHER ISSUES NOT DISCUSSED ELSEWHERE IN THIS PREAMBLE

A. RISK ASSESSMENT (§ 1990.111(j))

Risk assessments may involve two elements: the qualitative identification of the existence and nature of a risk, and the quantitative estimation of its possible magnitude and likely distribution among exposed persons. The nature of the risk assessment possible will necessarily vary from substance to substance. The scientific bases for quantitative estimates of the cancer risks to workers exposed to potential occupational carcinogens are reviewed in detail in Section VIII. On the basis of voluminous expert testimony in the Record, OSHA concluded that the uncertainties involved in such estimates are far too large to justify using them as the basis for setting a permissible exposure limit, (see sections VIII and XI.) This conclusion was well illustrated by the more than million fold variation in the estimates of risks presented by various scientific authorities for risks to workers exposed to vinyl chloride at the OSHA standard of 1 ppm. Nevertheless, OSHA concluded that risk assessments may be useful for two purposes: (a) to predict relative risks of different carcinogens when extensively studied as the basis for establishing priorities; (b) to estimate reduction in risks as a result of regulatory action, when adequate data exist to assess the role of the many factors that lead to uncertainties.

Accordingly, in appropriate circumstances, OSHA will attempt to make both qualitative and quantitative assessments of risk for individual substances where available data permit. In light of our interpretation of the Act and because of the enormous uncertainties involved in risk estimation, which are fully discussed in Section VIII, OSHA's estimates of possible risk will not be used to justify the establishment of any particular permissible exposure level, or to imply that any level of risk is judged to be "acceptable." It is clear from the evidence presented in the Record that at the present stage of scientific development, such estimates are so uncertain that reliance on a numerical cost/benefit calculation to set permissible exposure levels would be misleading. OSHA's assessments of risk will instead be intended to provide very rough estimates of the possible magnitude of the risks that may remain even after exposure has been reduced to the lowest feasible level. Such information will be of use for a number of purposes: to judge the likely effectiveness of the regulation and OSHA's compliance with the Act; to inform workers of possible risks and employers of possible liabilities; to help determine the need for long-term follow up of exposed workers; and, in cases in which residual risks appear high, to prompt a search for more effective control measures and for suitable substitutes. OSHA is aware that understatement of residual risk would be very dangerous. Accordingly, OSHA will use prudent and cautious techniques of risk estimation which will be designed to avoid understating the risks. In particular, for the reasons specified in detail in Section VIII, OSHA will use conservative mathematical techniques to extrapolate risks to low doses, and will use cautious assumptions if extrapolation from animals to humans is attempted. If risk estimates are based on human epidemiologic data, prudent and cautious assessments of exposure levels will be used, and attempts to extrapolate from partial-lifetime data to estimate lifetime risk will be made, except in cases in which there are

insufficient data to support such calculations.

B. SUITABLE SUBSTITUTES (§1990.111(k))

The Cancer Policy proposal included a requirement providing for no occupational exposure to Category I toxic substances where suitable substitutes exist that are less hazardous to humans. The "no occupational exposure requirement" proposed was not intended to be a ban on the use of the material. The substance could still be used, if necessary, utilizing a truly closed system. The basis for this provision is the widely accepted scientific conclusion that at the present time there is no satisfactory scientific way for demonstrating a safe level of exposure to a carcinogen (42 FR 54174). Therefore it is prudent public health policy to eliminate occupational exposure when suitable substitutes exist.

There was substantial comment on this requirement. The Natural Resources Defense Council recommended that no occupational exposure be permitted to carcinogens when safer substitutes were available, because of the generally accepted scientific principle that there is no safe level of exposure to a carcinogen. In addition, it recommended that no occupational exposure be permitted to a carcinogen, even if there were no suitable substitute, if that chemical does not have critical importance. However, it suggested that OSHA, in general, define the terms used in greater detail (C. II–270, p. 38; P.H. Brief, Ex. 268, p. 40; Tr. 6316–19).

The AFL–CIO and USW also supported this proposal. They pointed out the importance of substitution as a control technology (P.H. Brief, Ex. 261, pp. 96–99) and quoted from Dr. Melvin First, an industrial hygiene expert testifying for the American Petroleum Institute, who stated:

> "For an airborne carcinogen? I think we all agree that the first step is to see if there are suitable substitutes which are not carcinogenic and do not have other undesirable properties. This is a concept which has enormous appeal to our field of endeavor because it is such a neat and beautiful way to solve a problem." (Tr. 6862–3)

Mr. Mark Stepp, UAW, recommended substitution and engineering controls as the most effective control strategies (Tr. 5725).

Dr. Samuel Epstein pointed out that because of risks from carcinogens, claims that they serve unique purposes should be critically examined, and that even it they are useful, consideration should be given to banning or requiring their use in a closed system with continuous monitoring (S. V–37, p. 66). Dr. Sidney Wolfe (HRG) proposed that since there is no safe level of exposure to a carginogen, zero exposure should be the norm, with a permit system to prevent unnecessary use (Tr. 6452–54).

DuPont (S. III–134) discussed their own internal policy for controlling occupational exposures and recommended an alternative to OSHA's policy. Although they questioned OSHA's legal authority to require no occupational exposure when suitable substitutes exist (p. ii), they stated that they "are committed to closing down any process when safe operation is not possible." (p. 2) They discussed in Appendix B, pp. 3–8, their efforts to control a chemical, HMPA. Initially they controlled exposure to 100 ppb (parts per billion). Later animal data indicated that HMPA caused malignant tumors at very low exposures and immediate efforts were taken to reduce exposure within one year to 0.5 ppb. In addition a 4-year program to develop and replace HMPA with a suitable substitute was commenced. Dupont stated that this program has been successful.

A number of the industrial participants at the hearing criticized the suitable substitutes provision. These criticisms were summarized at considerable length in AIHC's Post Hearing Brief (Ex. 251A, pp. 68–81). These participants believed that OSHA did not adequately define the term "suitable substitute." They argued that if no occupational exposure was permitted, when substitution was technically possible but much more expensive and less satisfactory technically, great disruption would be created. Further it was pointed out that even a truly closed system would result in some exposure. As analytic techniques constantly improve, the no occupational exposure limit would, they believed, be a constantly shifting requirement. Further, they argued that market forces would lead to substitution anyway, if truly suitable substitutes existed for a carcinogen.

A number of companies and industry representatives discussed what they considered to be the results of setting a "no occupational exposure" level for specific chemicals. They suggested that in some circumstances great disruption would be created because there was no technically satisfactory substitute. In the case of other chemicals, they suggested that substitution was technically acceptable but would either be very expensive or moderately expensive. A number of the specific examples presented are discussed below.

The Snell Report (S. III–104 R&S, Ex. 66) presented by the AIHC, considered several specific instances of possible substitution. It concluded that:

> * * * Substitution potential varies with the specific applications for each substance. Complex technical and economic issues are involved in each substitution situation. A simple cost trade-off can influence the substitution potential if compliance costs raise the price sufficiently to motivate or shift to alternative chemicals. Substitution however, would be dramatically costly and disruptive if forced where no technological alternative exists. * * * (Ex. 66, p. 25)

Snell also concluded that,

> Substitution efforts, required or encouraged under this proposal, will require increased research and development efforts and a significant amount of time to accomplish. To the extent this occurs it can have a major negative effect on innovation. (S. III–104R, ID–2)

The attorneys for AIHC argued that OSHA does not have legal authority to set a "no occupational exposure" level. They contended that this is tantamount to a ban of a product. (Ex. 251A, p. 68 et seq.) They stated that there was no express language in the OSHA Act referring to banning substances and argued that statutes which permit bans contain express authority. They also contended that the suitable substitute provision in the proposal was too vague and that there were other legal problems with the proposal.

The AFL–CIO and United Steel Workers attorneys argued that OSHA does have legal authority to set a "no occupational exposure level" for a carcinogenic chemical if a suitable substitute exists (Ex. 261, p. 96 et seq.). They stated that substitution is a well recognized control procedure authorized by § 6(b)(7) of the OSHA Act.

OSHA has considered the extensive factual, policy and legal arguments on this point and the evidence presented. OSHA has concluded that substitution is the most effective control for occupational carcinogens and that it should be encouraged where it is feasible through a requirement for "no occupational exposure". OSHA believes that much of the criticism of such a policy was based on a misunderstanding. The proposal did not intend to encourage substitution by setting a "no occupational exposure level" where substitution is not feasible, just as engineering controls would not be imposed if they were not feasible. Further, neither the proposal nor the final regulation permit a "no occupational exposure" level to take effect until after a full hearing takes place, where all evidence will be carefully considered. The language of

the suitable substitutes sections has been changed to clarify the intent and to respond to the valid criticisms and suggestions made.

Substitution has always been considered the preferred control strategy for toxic or carcinogenic substances. It completely eliminates the hazard without extensive control devices and eliminates the possibility of unintended exposures from the breakdown of equipment. This control strategy is even more desirable in the case of carcinogens, where there is a substantial body of opinion that there is no completely safe level of exposure. See the discussion above, in Section V.D. 10.

The desirability of substitution of safer alternatives for toxic chemicals has been the first principle of industrial hygiene for many years. The industrial hygiene witnesses at this hearing reaffirmed this principle in their testimony, as analyzed in the engineering controls discussion in Section X. This testimony included that of industrial hygiene experts, such as Dr. First, who were invited to testify by industry. DuPont also pointed out that substitution is the appropriate approach when a chemical cannot be used safely as the HMPA example indicates.

Encouraging substitution by setting a "no occupational exposure level" when suitable substitutes are available is permitted and encouraged by the OSHA Act. It is a "control * * * procedure" authorized by § 6(b)(7) designed to encourage "the highest degree of health and safety protection for the employee" as mandated by § 6(b)(5) of the OSHA Act. It is feasible because before this control strategy may be implemented by this regulation, the evidence on the record must show that substitution is "feasible" as is also required by the Act. This control strategy does not ban the use of the carcinogenic chemical. While it encourages substitution by setting the "no occupational exposure" level, it does permit its use if the employer is able to design and prefers to use closed system engineering control technology to achieve this level of exposure, as it is defined below. However, the feasibility of the no occupational exposure level is judged by the feasibility of substitution, not by whether the employer may be able to design a truly closed system.

One of the criticisms of the proposal was that the term "suitable substitute" was too vague. Paragraph 1990.111(k) in the final regulation expressly clarifies that the determination of whether a suitable substitute exists requires consideration of the following factors.

Consideration must be given to evidence on the safety of the substitute. Data that would indicate this might be, for example, no valid positive tests indicating carcinogenicity of the substitute and a negative result in an animal test or several negative short term tests of the substitute. Consideration would also be given to the comparative acute and chronic toxicity of the carcinogenic chemical and the substitute, and other relevant factors, such as environmental factors.

Secondly, consideration must be given to the technical feasibility of the substitute including its relative effectiveness. A substitute, to be technically suitable, must perform reasonably well in the relevant functions. It need not, however, have the same performance characteristics of the chemical that it would be a substitute for, nor perform equally well in every aspect. This is essentially a factual determination and the examples discussed below provide good illustrations of what are and what are not technically suitable substitutes.

Thirdly, the economic cost of substitution must be considered. If the substitute is only moderately more expensive for a high or low volume chemical, then substitution is likely to be feasible. Similarly, if the substitute is substantially more expensive, but the chemical only makes up a small part of the cost of the final product, then substitution is also likely to be feasible. In these circumstances there are not likely to be major impacts on users. However, if the proposed substitute is substantially more expensive and makes up a large part of the cost of the final product then substitution may not be economically feasible. Also, if many of the producers of the product can switch to producing the substitute, or if its production is not the major part of most producers' product lines, then substitution is likely to be feasible in this respect. However, if most producers cannot switch to other products and it is a major part of most producers' product lines, then in some circumstances substitution may not be feasible.

The Cancer Policy makes no final determination on these issues for specific chemicals. Ultimate decisions will be based on all the facts involving a particular substance after a full hearing. Other factors may be relevant depending on the facts of a particular situation; the examples discussed below illustrate these criteria.

Consideration of the feasibility of the substitute also is to take into account the amount of capital investment needed to switch to the substitute and the time needed to install new equipment in an orderly fashion. These factors can often be met by permitting a reasonable phase-in time period for switching to the substitute. Sections 1990.111(k) and 1990.146(1) require that consideration be given to these matters and that a reasonable time period be set for substitution before the "no occupational exposure" requirement takes effect.

Industry representatives presented a number of examples of substitution which they argued indicated that "the no occupational exposure when suitable substitutes exist" provision would be unworkable. However, proper analysis of those examples, based upon the criteria for determining whether suitable substitutes exist which are set forth in the final regulation, shows that the suitable substitute provision is a sensible and feasible method of protecting employee health. The specific industry contentions of damaging consequences from substitution only occur in situations where no suitable substitutes in fact exist. In those circumstances, this regulation would not set a "no occupational exposure" limit and therefore those alleged difficulties would not occur. (The discussion of the following examples is not meant to imply that the chemicals considered would or would not be found to be potentially carcinogenic. They are discussed because various witnesses presented them as examples where substitution would be difficult.)

The example presented by the Refractories Institute was use of coal tar pitch in the manufacture of furnace linings and muds for sealing blast furnaces. According to the Institute, substitutes dramatically shorten the life of furnaces between relinings and could lead to unsafe blowouts of blast furnaces. If this evidence is correct, then clearly the substitutes are not suitable substitutes technically, and a "no occupational exposure" standard for coal tar pitch in these uses would not be permitted by this regulation. Dr. Knowlton of the Refractories Institute testified that there was no suitable substitute for coal tar pitch in the above uses (Tr. 6458).

A similar analysis applies to the examples presented in the Charles H. Kline & Co. study presented by Shell (S. III–83). They stated that the presently conceivable substitutes which might replace phenolic resins in the manufacture of plywood are much weaker and are not nearly as weather resistant. If that is true, then there would not be any technically suitable substitute for phenolic resins made from benzene, and there would be no basis for setting a "no occupational exposure level" for the benzene used for the purpose. Consequently, the drastic

consequence discussed by Kline from the "banning" of benzene in that use would not occur.

The other examples in the Kline study also appear to represent situations where suitable substitutes do not exist at the present time and therefore the regulation would not permit setting a "no occupational exposure" level. This was recognized by Shell itself. Dr. Sagenkahn of Shell stated in regard to the plywood example that "the intent here was really to show what the extreme could be." (Tr. 5586). This further response was also made:

Q. "Don't you think it would have been a more useful analysis (referring to the Kline study) if instead of taking situations where there really are not feasible substitutes and giving the analysis of them, you would have taken situations that would have been more arguably the case that there were feasible substitutes, to see what the effect of such a provision would be."

A. Dr. Sagenkahn: "Well, I would agree that might have been useful, but we could not perceive in advance what the result might be. You must remember that what we did is we went out and we asked people what they thought might happen so we could not know in advance that we either picked a good or bad example, and I agree that if we had found something where there was a suitable substitute, that might have been something in the other direction." (Tr. 5587)

The Snell Report's (S. III–104 R, S) discussion of substitution also provides some useful illustrations of the suitable substitutes requirement. Tetrachlorethylene (perchlorethylene) is widely used as a drycleaning agent and degreaser. In those uses the lowest technically feasible level of control appears at this time to be relatively high, in the multiparts per million. Many employees (and others) are exposed to this compound. If studies clearly indicate that tetrachlorethylene is a Category I carcinogen,[1] then it would seem approriate to reduce exposures below the level technically achievable with engineering controls.

Fluorocarbon drycleaning agents seem to have advantages and disadvantages in comparison with tetrachlorethylene, but overall appear to be reasonably suitable substitutes technically, at least as indicated by the discussion in Snell. Reasonable evidence of their safety and their permissibility under other acts and regulations would have to be considered before analysis of their suitability as substitutes would be taken further.

However, the Snell Report indicates it would cost approximately $30,000 in capital expenditures per average drycleaning establishment to switch. Many such establishments are small businesses and Snell suggests it would be difficult for them to raise the necessary capital even though the substitution might result in increased productivity. If this information supplied by Snell is correct, then there would be some feasibility questions about the suitability of the substitute. At the § 6(b) hearing on the regulation all the information on this point would be considered. The evidence might indicate that substitution would be feasible if a sufficiently long switchover time were permitted. (If replacement by a safer process takes place when equipment is normally replaced, then the actual additional cost of the switch may be small.) Alternatively, the evidence presented might indicate that another course of action was more appropriate.

Another example presented by Snell was n-propanol. Here for some uses the substitutes were, in Snell's opinion, clearly technically feasible, and Snell did not indicate that any major economic dislocation would occur from the switch. The substitutes are somewhat more expensive than n-propanol, but the substitutes are just a small part of the cost of the ultimate product. (If a substance which represents 1% of the cost of a final product goes up 25%, then the cost of the final product goes up an insignificant ¼ of 1%). A few chemical companies would have to switch production of one of their chemical lines, or the business of some would go down a small amount, balanced by a small increase in the business of other chemical companies, with no net employment changes. If the evidence indicates that n-propanol is a Category I Carcinogen and the evidence presented by Snell is correct on the feasibility of substitutes, then it appear that this may be a situation where it would be appropriate to permit no occupational exposure for some uses of n-propanol because suitable substitutes are available. This is an hypothetical analysis based on the data submitted by Snell. Obviously if a standard were proposed, the factual situation would be investigated in detail.

In summary then, OSHA believes that the criteria included in this final regulation for determining whether a "no occupational exposure" requirement shall issue for a use of a Category I carcinogen are clear, specific and reasonable. This is illustrated by the examples and discussion above. Further no determination to issue such a requirement will occur before an opportunity for an extensive evidentiary hearing. Therefore the criteria set forth in this section will be applied in the context of an extensive factual record which will give additional meaning to the issues and terms. In view of the substantial health benefits of encouraging substitution for carcinogenic chemicals where a safe level of exposure cannot be demonstrated, and in view of the detailed analysis that the final regulations requires to assure that the "no occupational exposure level" will only be set when it is feasible, OSHA has concluded that the "no occupational exposure" requirement will substantially improve occupational health, is feasible and will not have the negative effects alleged by some witnesses.

Some participants to this proceeding urged that OSHA go further than its proposal. Dr. Epstein recommended banning carcinogens in some circumstances (S.66). The Health Research Group recommended a permit system (Tr. 6452–54) and the NRDC recommended setting a "no occupational exposure" level even when suitable substitutes were not available, if the substance was not of crucial national importance (II–270, p. 38). NRDC noted that there is some legal authority which supports their suggested course of action. See *AFL–CIO* v. *Brennan*, 530 F.2d 109,121 (3d Cir., 1975).

For the reasons discussed in this section OSHA believes the provisions on suitable substitutes included in the final cancer policy are the most appropriate at this time. They will improve workers' health and will not create the administrative difficulties of a permit system or require consideration of the extent to which the social utility is relevant to OSHA standards setting. Therefore, it has not been necessary for OSHA to consider what additional authority it might have in this area. If there are circumstances in the future where the factual situation, additional policy considerations, or experience with the provision promulgated, indicate that directly banning a substance or creating a permit system might be warranted, OSHA will then consider whether either of these actions is authorized and appropriate. Any proposal premised on these options would of course be subject to the close scrutiny of full rulemaking proceedings.

There was a final major criticism of the "no occupational exposure" requirement, that the proposal had not adequately defined what OSHA meant by that level, except to say that a "truly closed system" must be used. Some also argued that without defining the concept

[1] This discussion should not be taken to indicate that the studies indicate or do not indicate that it is, but is rather a hypothetical discussion of substitutability based on evidence submitted by the AIHC.

of "no occupational exposure", the level set would be a constantly moving target as analytic techniques improved.

OSHA does not believe that the concept of a closed system is as elusive as some industry representatives have argued. Duncan Holaday, an industrial hygienist, testified that it was a term which was meaningful, and he gave examples (Tr. 2755–2760).

However, OSHA accepts the arguments that to be workable and enforceable, a numerical value must be set for the level of a substance which satisfies the requirement of "no occupational exposure." OSHA has considered several possible generic definitions, but has concluded that circumstances are likely to be different for different substances and that a specific upper limit should be set for each substance, on the basis of evidence generated in the record of the specific rule-making. In general, the simplest operational definition would be the lowest level detectable in an industrial environment with existing analytical technology. OSHA anticipates that in most cases such a level will be established on the basis of evidence in the record. However, there may be circumstances in which the analytical methodology is poorly developed, and such a level might not be low enough. In such a case OSHA might set a lower level based on other concrete and specific methodology, e.g., by the use of tracers or surrogate substances.

Section 1990.146(1) requires that an employer who chooses not to use the suitable substitute, must achieve compliance with the level set for the carcinogen with engineering and work practice controls alone. As discussed in Section X, respirators are a much less satisfactory method to control exposures for carcinogens. When a suitable substitute exists, it is inappropriate to permit the employer to achieve compliance with respirators.

The Snell Report suggested (S. III–104R, p. ID–2) that encouraging substitution would require increased research and development efforts and would have a negative effect on innovation. OSHA hopes that this requirement will indeed encourage additional research on safer substitutes and enhance technological innovation. OSHA believes that increased research and development on safer chemicals is extremely important, and to the extent this provision encourages it, OSHA believes that this is a further justification for it.

The second part of the Snell statement is speculation. Snell presented no evidence at all on how increased safety regulation has stifled innovation. Indeed, the only concrete evidence in this record indicates to the contrary. As a result of the OSHA vinyl chloride standard, industry increased research, which resulted in the development of better stripping techniques (methods of removing the carcinogenic monomer from the final product) and safer and more efficient production techniques. These facts were acknowledged by Snell itself at the hearing. After a lengthy discussion of the vinyl chloride example, the following question and answer took place.

Q. "So as a result of OSHA pushing the chemical companies, we have now developed better technology at low cost to achieve low levels."

A. Mr. Grisser (Snell): "That is correct." (Tr. 3908)

It is OSHA's understanding that a number of those newly developed techniques have proved useful in controlling exposures to acrylonitrile at lower cost as well.

Several witnesses stated that market forces will tend to lead to voluntary substitution when low levels of exposure are needed for one chemical and a safer, suitable substitute is available. That is certainly correct. However, the dangers from carcinogens are great and the advantages of substitution as a control strategy are substantial, as discussed above. Therefore, OSHA believes it is appropriate to go somewhat further than market forces to encourage substitution, even though, for example, the substitute may be somewhat more costly than the carcinogen after controls are instituted.

Finally, it has been argued that the "no occupational exposure" provision of this regulation is somehow inconsistent with Section 6 of the Toxic Substances Control Act (TSCA). The contention made is that since TSCA gives the EPA authority to ban the production and use of a chemical which creates unreasonable risk of injury to health, it is inconsistent that OSHA have authority to "ban" a substance. OSHA finds no inconsistency between TSCA and the "no occupational exposure when a suitable substitute exists" provision of the Cancer Policy final standard. First, the OSHA regulation does not ban a substance, but generally sets exposure at the lowest detectable level. Secondly, nothing in the OSHA regulation would prevent the EPA from banning the production and use of the chemical under TSCA criteria, if they were met. Third, no regulatory conflict would result if OSHA set a "no occupational exposure level", and EPA decided not to prohibit the manufacture of the substance. It could still be manufactured under the OSHA regulation, but employees could not be exposed above the "no occupational exposure level" set.

It is also contended (AIHC, Post Hearing Brief, Ex. 251A, pp. 79–80) that the pre-marketing notification requirements of section 5 of TSCA would make it impossible to introduce a suitable substitute in the time frames required by OSHA regulations. Section 5 of TSCA requires manufacturers to notify EPA prior to the introduction of a new chemical or in some circumstances a new use of an old chemical. In certain circumstances, the manufacturer must undertake testing and submit the new test data. In other circumstances the EPA may request an injunction to prevent the use of a chemical presenting an unreasonable risk of injury.

There is no inconsistency between the TSCA and the OSHA Act and the Cancer Policy final standard in this respect. Section 1990.111(k) provides that the time permitted before the no occupational exposure requirement takes effect must be sufficiently long to take into account regulatory requirements such as the provisions of TSCA. Further, any such regulation will by law have to be contingent on EPA not taking action to prevent the use of the substitute. If for some reason EPA takes action to prevent the new use of the suitable substitute, then the "no occupational exposure limitation" of the standard would not take effect since no suitable substitute would exist. In practice it would be unlikely that EPA would make a determination that a chemical, which OSHA has found to be a suitable substitute, presented an unreasonable risk of injury. OSHA will take into account evidence of the safety of the substitute before setting a no occupational exposure level.

C. POLICY OF AT "NO COST" TO EMPLOYEES

OSHA is explicity incorporating in the Cancer Policy the regulatory policy that where employers are required to provide medical surveillance and/or personal protective equipment in standards initiated pursuant to this Cancer Policy, that these medical examinations or protective equipment be provided at no cost to the employee.

The requirement that these protective elements be provided at "no cost" to employees was included in the relevant model provisions in the proposal. This aspect of these provisions generated virtually no comment.

Most standards regulating exposure to toxic substances, including carcinogens have incorporated such provisions. See e.g. for medical surveillance;

§ 1910.1017(k), vinyl chloride;
§ 1990.1018(1)(ii), inorganic arsenic;
§ 1910.1028(1)(ii), benzene;
§ 1910.1029(j)(1)(iv), coke oven emissions. As to personal protective equipment, see the following:
§ 1910.1018(j)(1), inorganic arsenic;
§ 1910.1044(j)(1), DBCP; and
§ 1910.145(j)(1), acrylonitrile.

The reasons for adopting this as policy for medical surveillance, are the following. Congress has instructed OSHA that where appropriate "standards shall prescribe the type and frequency of medical examinations or other tests which shall be made available, by the employer or at his cost, to employees exposed to such hazards in order to most effectively determine whether the health of such employees is adversely affected by such exposure" (§ 6(b)(7)).

OSHA believes that this statutory mandate alone, is a sufficient basis upon which to declare that medical surveillance must be provided without cost to employees. In any event, even without such explicit authority, it would be appropriate to impose this requirement in order to effectuate complete medical surveillance, and hence to further the purposes of the Act. The agency found in the recent lead rulemakings that a primary reason that many employees were reluctant to participate in medical surveillance programs was the fear of resulting adverse economic consequences, such as transfers or job termination. (See preamble to the lead standard, 43 FR at 54442–54450).

Employees may also be reluctant to participate in medical examinations because cancer is a particularly feared disease. Given these existing disincentives to employee participation in medical examination programs, it plainly would be counterproductive to add yet another—the cost of the examinations themselves. Consequently, if the medical surveillance provisions under the Cancer Policy are to provide meaningful employee protection, employers must bear the costs.

Similarly, the cost of personal protective equipment could be an economic disincentive to employees which would reduce the efficacy of personal protective equipment provisions. Such protection is of course an essential element of an occupational health program designed to eliminate exposure to carcinogens, and thus specifically required when appropriate, under section 6(b)(7).

OSHA notes that the proposition that the cost of employee protection against occupational health hazards is properly placed on the employer has received significant judicial endorsement. (See most recently *AFL-CIO* v. *Marshall* s78–1562 U.S.C.A. D.C. Slip at 79.) It is also consistent with Congressional recognition that the primary responsibility for compliance with the Act is on the employer (Leg. Hist. 150–151).[1]

Finally, the requirement that employers pay for protective equipment is a logical corollary of the accepted proposition that the employer must pay for the institution of required engineering and work practice controls. To the extent that protective equipment like engineering controls, is intended also to protect against airborne contamination, employers logically must pick up the expense. There is no rational basis for distinguishing the use of personal protective equipment to protect against other means of contamination such as spills, or protect against other routes of exposure (absorption, rather than inhalation). The goal, in each case, is employee protection; consequently, the responsibility of paying for the protection should, in each case rest on the employer. Based on our review of this record, our recent experience with other health standards, and our evaluation of what is necessary and appropriate to effectuate the statutory purposes, we conclude that the proper approach for the agency on the promulgation of new standards is to require employers to pay for all personal protective equipment.

D. MEDICAL REMOVAL PROTECTION

A medical examination may reveal that an employee should be removed from an area where there is the possibility of contact with a carcinogen. It may also reveal that an employee should not wear a respirator, which he may need to wear because he is assigned to an area with high exposure levels of the carcinogen. Medical removal protection (MRP) would provide that when an employee has to be removed from his assigned work area in these circumstances, the employer must assure that the employee receives the same rate of pay and does not lose seniority. The employer may do this by assigning the employee to another area where exposures are lower and by maintaining the employee's pay and seniority from his old position until such time as the employee's condition improves.

Union representatives pointed out the importance of medical removal protection in this proceeding (Ex. 184–c, pp. 3–4). Employees might refuse to take medical examinations because they would fear that an adverse medical opinion could result in loss of employment. As a result, the purpose of the medical surveillance requirements would be defeated and early detection of illness would, too often, not occur.

OSHA agrees with the importance of not creating disincentives to taking medical examinations. Medical removal protection has been included in two recent OSHA standards, lead and cotton dust, where a substantial amount of evidence was introduced on how to appropriately design a medical removal protection program.

The Cancer Policy proposal concentrated on scientific, industrial hygiene and procedural issues, and did not specifically raise the issue of MRP. Relatively little data was introduced into the record to assist in designing an MRP program. Therefore, OSHA believes that it would not be possible to include MRP in the final Cancer Policy at this time.

However, medical removal protection may be included in proposals for the regulation of individual carcinogens pursuant to the Cancer Policy as an additional regulatory provision which is appropriate in the specific circumstances of that chemical. In addition, OSHA is investigating the possibility of proposing a general medical removal protection regulation which would apply to toxic and carcinogenic chemicals. During a rulemaking on such a proposal it would be possible to concentrate on MRP and to design an effective program based on a careful review of the relevant information.

E. ALTERNATIVE PROPOSALS

This preamble is organized by issue. Each section discusses the proposals' provisions, the evidence and views presented and OSHA's conclusions on each issue. In addition, several participants submitted comprehensive alternative approaches. The major provisions of the alternatives are considered under the appropriate issues and the regulatory aspects of the proposal and alternatives are summarized in the Final Environmental Impact Statement. This section gives a brief overview of the major alternatives, a summary of OSHA's views on their major provisions and cross references to other sections of the preamble which discuss those issues in depth.

[1] The Act's overriding purpose is to "assure so far as possible every working man and woman in the nation safe and healthful working conditions." Section 2(b) of the Act, 29 U.S.C. s651(b) 1979. See also Legis. Hist. at 1050–51 (remarks of Sen. Eagleton) (costs of health and safety standards are reasonable and necessary costs of doing business); id. at 1051 (remarks of Rep. Broomfield) workers should not suffer while labor and industry argue).

The major alternative approaches were submitted by the American Petroleum Institute and the American Industrial Health Council. Dupont's is similar to AIHC's. Union and environmental groups supported OSHA's proposal in large part but made varying suggestions on the different components.

API's Alternative

The API's approach provided no formal categorization scheme. Instead API suggested that OSHA perform extensive evaluations using all scientific evidence and risk-benefit data on substances with carcinogenic potential to establish overall priorities for regulation. The extent and kind of regulation would also be based on the result of the risk assessment.

Rather than classification criteria, API also suggested that a "hierarchy of results" of animal and human evidence should be considered as "guidelines" for priorities and classifications. All scientific information and policies would be evaluated prior to the regulation of each chemical.

OSHA believes that risk assessment may provide some assistance in setting priorities. OSHA, in response to suggestions by API and many others, has adopted a prioritization framework. These issues are discussed in Sections VIII, IX and XIIB.1 and 7. Also, OSHA believes that by leaving open for reconsideration all scientific policies during the regulation of each chemical, the API approach will not increase the speed of the regulatory process, a necessary goal of this policy as discussed in Section II.

Rather than adopting consistently applicable criteria, API suggested a "summary judgment" type of proceeding in each rulemaking. OSHA would accompany proposed standards with statements of 1) uncontroversial material facts and 2) material issues not currently susceptible to factual resolution. Parties could dispute these conclusions by submitting supporting evidence. OSHA would determine whether its motion for summary judgment had been effectively opposed. To the extent it had not been effectively opposed, OSHA could regard the issue as settled. Judicial review of OSHA's denial of an opposition to OSHA's summary judgment would lie at the time of appeal of the final standard.

OSHA believes the "summary judgment" procedure is less appropriate and less fair than "generic rulemaking" to apply policy to the regulation of carcinogens. A summary judgment procedure is inappropriate to establish broad general scientific policies because less scientific expertise can be concentrated on the issues. Also, it would be more difficult for parties interested only in the policy to participate, and the application of a policy may vary from proceeding to proceeding.

The API alternative recommended a more flexible approach to the inclusion of model standards provisions for particular chemicals. This would depend on the specific characteristics of each substance. OSHA has incorporated many of these suggestions into the final Cancer Policy as is discussed in Section X A.

AIHC's Alternative

AIHC's process to identify carcinogens would be conducted by a Scientific Review Panel, which was outside OSHA and was composed of both governmental and non-governmental experts. OSHA did not accept this suggestion, because it believed it was a non-accountable process, inconsistent with the legislative history, and for legal reasons. These are discussed in Section IX.C.

The panel, the sole body authorized to scientifically evaluate evidence, could propose revisions of AIHC's categorization scheme or criteria, which would then be subject to APA informal rulemaking.

Classification of carcinogens under the AIHC scheme would be based on generically determined criteria. Three categories were suggested. Category I was "known human carcinogens." Category II was "confirmed animal carcinogens." Classification in Category II would require positive animal tests in two different species where "excessive doses" were not administered and there was "an appropriate route of administration." Within categories I and II were subcategories depending on the "potency" of the carcinogen. Category III would include chemicals for which animal bioassays show positive results but do not meet Category II criteria.

OSHA believes that its classification framework has a sounder scientific basis. See the discussions in Sections V.D. 3, 8 & 9, VIII, and IX. F.

The AIHC recommended that there be no required regulatory response. The decision to issue an ETS upon Category I classification, was to be made "as soon as possible." It would turn on whether OSHA decided a "grave danger" under § 6(c) existed. If an ETS did not issue, a proposal for a permanent § 6(b) standard would be considered. It would depend on OSHA's regulatory priorities, and whether OSHA decided that a standard was "necessary" to protect employees. The determination of "necessity" would hinge on risk/benefit analysis.

The permissible exposure limit in the AIHC alternative would be based on the concept of an "acceptable" exposure level derived from risk/benefit analysis. Risk/benefit analysis also would be used in considering each regulatory provision in a proposal. To the extent AIHC's scheme relies on risk assessment and risk/benefit analysis to set exposure levels, the discussion in Sections VIII and XI is applicable.

The final Cancer Policy includes some provisions similar to AIHC's suggestions. The issuance of ETS's would depend on the specific circumstances (§ IX. H.). A priorities system has been included and risk assessment data is one factor to be taken into account in setting those priorities (§ IX. 6.).

AFL–CIO–USWA Alternative

AFL–CIO–USWA generally endorsed OSHA's classification system and criteria. They recommended as an additional classification basis for Categories I and II, evidence showing the component's ability to metabolize in the body to a confirmed carcinogen. This has been incorporated in the Cancer Policy. See S. 1990. 143(k). Metabolism is discussed in Section V.D. 13.

OSHA's proposed Category I response was endorsed. An alternative response to Category II classification utilizing hazard alerts, program directives and enforcing under the general duty clause of Section 5(a) of the Act was suggested. OSHA has not included the latter suggestion in the framework of the Cancer Policy. However it has been considering modifying its enforcement policies to utilize similar strategies pursuant to the OSH Act.

The NRDC Alternative

NRDC endorsed in general OSHA's proposal. However, NRDC urged that a priority system be established to first control those substances posing the greatest carcinogenic risk. NRDC also urged that the generic scientific policies be separately listed and that specific amendment procedures be articulated in the Cancer Policy itself. These suggestions, also made by other participants, have been adopted. See the discussions in § IX. D, E, G, & I.

OSHA appreciates the participants who submitted alternative comprehensive approaches. They have assisted OSHA in modifying the proposal to achieve a more effective final Cancer Policy. Some of the provisions of the various alternatives have been incorporated into the final

policy and others have not, depending on the scientific evidence and OSHA's policy judgments discussed in this preamble.

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XIV. AUTHORITY

This document was prepared under the direction of Eula Bingham, Assistant Secretary of Labor for Occupational Safety and Health, and by Anson M. Keller, the Special Assistant for Legal and Regulatory Policy for the Occupational Safety and Health Administration and Grover C. Wrenn, Jr., Director of Federal Compliance and State Programs (formerly Director of Health Standards Programs) for the Occupational Safety and Health Administration, U.S. Department of Labor, 3rd Street and Constitution Ave., N.W., Washington, D.C. 20210.

The **Federal Register** has been requested to officially file this document at 1 p.m. E.S.T. on January 18, 1980 which shall be the time of issuance of this document as provided by 29 CFR § 1911.18. The time of issuance is the earliest moment that petitions for review may be filed with United States Courts of Appeals.

Accordingly, pursuant to sections 4(b), 6(b), 8(c) and 8(g) of the Occupational Safety and Health Act of 1970 (84 Stat. 1592, 1593, 1599; 29 U.S.C. §§ 653, 655, 657), the Secretary of Labor's Order 8–76 (41 FR 25059) and 29 CFR Part 1911, Chapter XVII of Title 29, the Code of Federal Regulations is hereby amended by adding a new health standard and procedural regulation for the Identification, Classification and Regulation of Potential Occupational Carcinogens, as Part 1990.

Signed at Washington, D.C., this 16th day of January, 1980. This amendment is effective on April 21, 1980.

Ray Marshall,

Secretary of Labor.

Eula Bingham,

Assistant Secretary of Labor for Occupational Safety and Health.

PART E. REGULATORY TEXT

A new Part 1990 is added to Title 29 of the Code of Federal Regulations, reading as follows:

PART 1990—IDENTIFICATION, CLASSIFICATION, AND REGULATION OF POTENTIAL OCCUPATIONAL CARCINOGENS

General

Sec.

1990.101 Scope.
1990.102 Purpose.
1990.103 Definitions.
1990.104 Scientific review panel.
1990.105 Advisory committees.
1990.106 Amendments to this policy.

The OSHA Cancer Policy

Sec.

1990.111 General statement of regulatory policy.
1990.112 Classification of potential carcinogens.

Priority Setting

1990.121 Candidate list of potential occupational carcinogens.
1990.122 Response to petitions.
1990.131 Priority lists for regulating potential occupational carcinogens.
1990.132 Factors to be considered.
1990.133 Publication.

Regulation of Potential Occupational Carcinogens

1990.141 Advance notice of proposed rulemaking.
1990.142 Initiation of a rulemaking.
1990.143 General provisions for the use of human and animal data.
1990.144 Criteria for consideration of arguments on certain issues.
1990.145 Consideration of substantial new issues or substantial new evidence.
1990.146 Issues to be considered in the rulemaking.
1990.147 Final action.

Model Standards

1990.151 Model standard pursuant to section 6(b) of the Act.
1990.152 Model emergency temporary standard pursuant to section 6(c) of the Act.

Authority: Secs. 4(b), 6(b), 8(c) and 8(g) (84 Stat. 1592, 1593, 1599, 1599; 29 U.S.C. §§ 653, 655, 657), The Secretary of Labor's Order 8–76 (41 FR 25059) and 29 CFR Part 1911, Chapter XVII of Title 29.

General

§ 1990.101 Scope.

This Part establishes criteria and procedures for the identification, classification, and regulation of potential occupational carcinogens found in each workplace in the United States regulated by the Occupational Safety and Health Act of 1970 (the Act). The procedures contained in this Part supplement the procedural regulations in other parts of this Chapter. In the event of a conflict, the procedures contained in this Part shall govern the identification, classification, and regulation of potential occupational carcinogens. This Part may be referred to as "The OSHA Cancer Policy."

§ 1990.102 Purpose.

The Act provides, among other things, that "the Secretary, in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his or her working life. Development of standards under this subsection shall be based upon research, demonstrations, experiments, and such other information as may be appropriate. In addition to the attainment of the highest degree of health and safety protection for the employee, other considerations shall be the latest available scientific data in the field, the feasibility of the standards, and experience gained under this and other health and safety laws. Whenever practicable, the standard promulgated shall be expressed in terms of objective criteria and of the performance desired" (section 6(b)(5)). It is the purpose of the regulations of this Part to carry out the intent of the Act with respect to the identification, classification, and regulation of potential occupational carcinogens.

§ 1990.103 Definitions.

Terms used in this Part shall have the meanings set forth in the Act. In addition, as used in this Part, the following terms shall have the meanings set forth below:

"Act" means the Occupational Safety and Health Act of 1970 (Pub. L. 91–596, 84 Stat. 1590 *et seq.*, 29 U.S.C. 551 *et seq.).*

"Administrator of EPA" means the Administrator of the United States Environmental Protection Agency, or designee.

"Chairperson of CPSC" means the Chairman of the United States Consumer Product Safety Commission, or designee.

"Commissioner of FDA" means the Commissioner of the Food and Drug Administration, United States Department of Health and Human Services, or designee.

"Director of NCI" means the Director of the National Cancer Institute, United States Department of Health and Human Services, or designee.

"Director of NIEHS" means the Director of the National Institute of Environmental Health Sciences, United States Department of Health and Human Services, or designee.

"Director of NIOSH" means the Director of the National Institute for Occupational Safety and Health, United States Department of Health and Human Services, or designee.

"Secretary of HHS" means the Secretary of the United States Department of Health and Human Services, or designee.

"Mutagenesis" means the induction of heritable changes in the genetic material of either somatic or germinal cells.

"Positive results in short-term tests" means positive results in assays for two or more of the following types of effect: (1) the induction of DNA damage and/or repair; (2) mutagenesis in bacteria, yeast, *Neurospora* or *Drosophila melanogaster;* (3) mutagenesis in mammalian somatic cells; (4) mutagenesis in mammalian germinal cells; or (5) neoplastic transformation of mammalian cells in culture.

"Potential occupational carcinogen" means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals.

§ 1990.104 Scientific review panel.

(a) *General.* At any time, the Secretary may request the Director of NCI, the Director of NIEHS and/or the Director of NIOSH to convene a scientific review panel ("the panel") to provide recommendations to the Secretary in the identification, classification, or regulation of any potential occupational carcinogen.

(b) *Membership.* The panel will consist of individuals chosen by the respective Director(s). The panel will consist of individuals who are appropriately qualified in the disciplines relevant to the issues to be considered, and who are employed by the United States. The panel does not constitute an advisory committee within the meaning of sections 6(b) or 7(b) of the Act, or the Federal Advisory Committee Act (Pub. L. 92–463, 86 Stat. 770).

(c) *Report.* The Secretary shall request that the panel submit a report of its evaluation within ninety (90) days after the appointment of the members of the panel. The Secretary shall place a copy of the report in the record of any relevant rulemaking undertaken pursuant to this Part and allow an appropriate time for public review and comment. If a panel is not established or fails to file a timely report, or if the Secretary determines that it is necessary to proceed without waiting for the panel's report, the Secretary may proceed in making any determination without such report.

(d) *Other aid and assistance.* Nothing herein precludes the Secretary from obtaining advice or other aid from any person or organization including NCI, NIEHS, and NIOSH.

§ 1990.105 Advisory committees.

The Secretary may appoint an Advisory Committee, pursuant to sections 6(b) and 7 of the Act, and 29 CFR Part 1912, concerning any potential occupational carcinogen. The Secretary shall require the Advisory Committee to submit its recommendations to assist the Secretary in standard setting no later than ninety (90) days from the date of the Advisory Committee's appointment, unless extended by the Secretary for exceptional circumstances. If an Advisory Committee fails to file a timely report, the Secretary may proceed in standard setting activities without such a report.

§ 1990.106 Amendments to this policy.

(a) *Initiation of review of this policy.*—(1) *Secretary's request.* No later than every three (3) years from the effective date of this Part, or from the last general review, the Secretary shall request the Director of NCI, the Director of NIEHS and/or the Director of NIOSH, to review this Part and render their opinions on whether significant scientific or technical advances made since the effective date of this Part warrant any amendment to this Part. The request shall ask that the answer be provided to the Secretary within one hundred twenty (120) days.

(2) *Recommendations by the institutes.* At any time, the Director of NCI, the Director of NIEHS and/or the Director of NIOSH may submit recommendations to the Secretary for amendments to this Part whenever any of them believes that scientific or technical advances justify such amendments.

(3) *Petitions from the public.* (i) Any interested person may petition the Secretary concerning amendments to this Part based upon substantial new issues or substantial new evidence.

(ii) For the purposes of this Part, substantial new evidence is evidence which differs significantly from that presented in establishing this Part, including amendments.

(iii) For the purposes of this Part, substantial new issues are issues which differ significantly from those upon which the Secretary has reached a conclusion in the rulemaking establishing this Part (including the conclusions reached in the preamble).

(iv) Each petition to amend this part shall contain at least the following information:

(A) Name and address of petitioner;

(B) The provisions which the petitioner believes are inappropriate;

(C) All data, views and arguments relied upon by the petitioner; and

(D) A detailed statement and analysis as to why the petitioner believes that the data, views and arguments presented by petitioner:

(i) Constitute substantial new issues or substantial new evidence; and

(ii) Are so significant as to warrant amendment of this Part.

(b) *Response to recommendations and petitions.*—(1) *By the institutes.* Whenever any Director recommends an amendment to this Part, the Secretary shall, within one hundred twenty (120) days after receipt of the recommendation, publish in the **Federal Register,** a notice which (i) states the reasons why the Secretary has determined not to commence a rulemaking proceeding to amend this Part, in whole or in part, at that time; or (ii) commences a rulemaking proceeding to consider amending this Part accordingly; or (iii) appoints an Advisory Committee as provided for by § 1990.105 of this Part and sections 6(b) and 7 of the Act.

(2) *By the public.* Within ninety (90) days, or as soon thereafter as possible, after receipt of a petition pursuant to section 1990.106(a)(3), the Secretary shall: (i) refer the petition to the Director of NCI, the Director of NIEHS and/or the Director of NIOSH, in which case the provisions of §§ 1990.106 (a) and (b)(1) are applicable; or (ii) appoint an advisory committee; (iii) deny the petition, briefly giving the reasons therefor; or (iv) commence a rulemaking proceeding to consider amending this Part accordingly.

(3) *On the Secretary's motion.* At any time, the Secretary may, on his own motion, commence a rulemaking proceeding to amend this Part.

The OSHA Cancer Policy

§ 1990.111 General statement of regulatory policy.

(a) This Part establishes the criteria and procedures under which substances will be regulated by OSHA as potential occupational carcinogens. Although the conclusive identification of "carcinogens" is a complex matter "on the frontiers of science," (*IUD* v. *Hodgson* 499 F. 2d 467, 474 (D.C. Cir. 1974)), responsible health regulatory policy requires that criteria should be specified for the identification of substances which should be regulated

as posing potential cancer risks to workers.

(b) The criteria established by this Part are based on an extensive review of scientific data and opinions. The Part provides for amending these criteria in light of new scientific developments. Decisions as to whether any particular substance meets the criteria or not will be consistent with the policies and procedures established by this Part and will be based upon scientific evaluation of the evidence on that substance.

(c) This Part applies to individual substances, groups of substances, or combinations or mixtures of substances which may be found in workplaces in the United States. In individual rulemaking proceedings under this Part, the identity and range of substances and mixtures to be covered by the standard will be specified and the appropriateness of applying the available evidence to the range of substances and mixtures proposed for regulation will be subject to scientific and policy review.

(d) Potential occupational carcinogens will be identified and classified on the basis of human epidemiological studies and/or experimental carcinogenesis bioassays in mammals. Positive results in short term tests will also be used as concordant evidence.

(e) Potential occupational carcinogens will be classified and regulated in accordance with the policy. The scientific evidence as to whether individual substances meet these criteria will be considered in individual rulemakings. The issues which may be considered in these rulemakings will be limited as specified herein.

(f) This policy provides for the classification of potential occupational carcinogens into two categories depending on the nature and extent of the available scientific evidence. The two categories of potential occupational carcinogens may be regulated differently.

(g) The policy establishes a procedure for setting priorities and making them public.

(h) Worker exposure to Category I Potential Carcinogens will be reduced to the lowest feasible level, primarily through the use of engineering and work practice controls. This is predicated in part upon the finding that no methods have been demonstrated for establishing exposure levels for carcinogens, acting singly or in combination, below which risks to exposed workers would be absent.

(i) Worker exposure to Category II Potential Carcinogens will be reduced as appropriate and consistent with the statutory requirements on a case-by-case basis in the rulemaking proceedings on individual substances. Any permissible exposure level so established shall be met primarily through engineering and work practice controls.

(j) The assessment of cancer risk to workers resulting from exposure to a potential occupational carcinogen will be made on the basis of available data. Because of the uncertainties and serious consequences to workers if the estimated risk is understated, cautious and prudent assumptions will be utilized to perform risk assessments. The form and content of the risk assessment will thus depend on the Secretary's judgment of the available data.

(k) Where the Secretary determines that one or more suitable substitutes exist for certain uses of Category I Potential Carcinogens that are less hazardous to humans, a no occupational exposure level shall be set for those uses, to be achieved solely through the use of engineering and work practice controls to encourage substitution. In determining whether a substitute is suitable, the Secretary will consider the technological and economic feasibility of the introduction of the substitute, including its relative effectiveness and other relevant factors, such as regulatory requirements and the time needed for an orderly transition to the substitute.

§ 1990.112 Classification of potential carcinogens.

The following criteria for identification, classification and regulation of potential occupational carcinogens will be applied, unless the Secretary considers evidence under the provisions of §§ 1990.143, 1990.144 and 1990.145 and determines that such evidence warrants an exception to these criteria.

(a) *Category I Potential Carcinogens.* A substance shall be identified, classified, and regulated as a Category I Potential Carcinogen if, upon scientific evaluation, the Secretary determines that the substance meets the definition of a potential occupational carcinogen in (i) humans, or (ii) in a single mammalian species in a long-term bioassay where the results are in concordance with some other scientifically evaluated evidence of a potential carcinogenic hazard, or (iii) in a single mammalian species in an adequately conducted long-term bioassay, in appropriate circumstances where the Secretary determines the requirement for concordance is not necessary. Evidence of concordance is any of the following: positive results from independent testing in the same or other species, positive results in short-term tests, or induction of tumors at injection or implantation sites.

(b) *Category II Potential Carcinogens.* A substance shall be identified, classified, and regulated as a Category II Potential Carcinogen if, upon scientific evaluation, the Secretary determines that: (i) the substance meets the criteria set forth in § 1990.112(a), but the evidence is found by the Secretary to be only "suggestive"; or (ii) the substance meets the criteria set forth in § 1990.112(a) in a single mammalian species without evidence of concordance.

Priority Setting

§ 1990.121 Candidate list of potential occupational carcinogens.

(a) *Contents.* The Secretary shall prepare a list of substances (the "Candidate List") which are reported to be present in any American workplace and which, on the basis of a brief scientific review of available data, may be considered candidates for further scientific review and possible regulation as Category I Potential Carcinogens or Category II Potential Carcinogens. For the purposes of this paragraph, "available data" means:

(1) The data submitted by any person;

(2) Any data referred to by the Secretary of HHS or by the Director of NIOSH, either in the latest list entitled "Suspected Carcinogens" or any other communication;

(3) Literature referred to in U.S. Public Health Service, Publication No. 149;

(4) Data summarized and reviewed in Monographs of the International Agency for Research on Cancer (IARC) of the World Health Organization;

(5) The Toxic Substances Control Act Inventory of Chemical Substances, published by the Administrator of EPA;

(6) The Secretary of HHS's Annual Report to the President and the Congress as required by the Community Mental Health Centers Extension Act of 1978, sec. 404(a)(9), 42 U.S.C. sec. 285.

(7) Any other relevant data of which the Secretary has actual knowledge.

(b) *Tentative classification.* The Secretary may tentatively designate substances on the Candidate List as candidates for classification as Category I Potential Carcinogens or as Category II Potential Carcinogens, or may list substances without a tentative designation, based on the brief scientific review of available data for the purpose of initiating a more extensive scientific review.

(c) *No legal rights established.* The inclusion or exclusion of any substance from the Candidate List shall not be

subject to judicial review nor be the basis of any legal action, nor shall the exclusion of any substance from the list prevent the regulation of that substance as a potential occupational carcinogen. The inclusion of a substance on the Candidate List and its possible tentative designation as a Category I Potential Carcinogen or a Category II Potential Carcinogen therein do not reflect a final scientific determination that the substance is, in fact, a Category I Potential Carcinogen or a Category II Potential Carcinogen. It is a policy determination based on the brief scientific review that the Secretary should conduct a thorough review of all relevant scientific data concerning the substance.

§ 1990.122 Response to petitions.

Whenever the Secretary receives any information submitted in writing by any interested person concerning the inclusion or omission of any substance from the Candidate List, the Secretary shall briefly review the information and any other available data, as defined in § 1990.121(a). The results of the Secretary's review shall be transmitted to the petitioner, together with a short statement of the Secretary's reasons therefor, and made public upon request.

§ 1990.131 Priority lists for regulating potential occupational carcinogens.

The Secretary shall establish two priority lists for regulating potential occupational carcinogens. One list should include approximately ten (10) candidates for rulemaking as Category I Potential Carcinogens; the other approximately ten (10) candidates for rulemaking as Category II Potential Carcinogens. The order of placement of substances on these lists will not reflect the Secretary's determination of the exact order in which these substances should be regulated in rulemaking proceedings but rather a policy determination that the Secretary plans to address some or all of these substances prior to proceeding with a thorough scientific review of data concerning other substances on the Candidate List. The inclusion or exclusion of any substance on these lists shall not be subject to judicial review or be the basis for any legal action. The Secretary may regulate a potential occupational carcinogen which has not been placed on these lists. The inclusion of a substance on either of these lists does not reflect a final scientific determination that the substance is, in fact, a Category I Potential Carcinogen or a Category II Potential Carcinogen.

§ 1990.132 Factors to be considered.

(a) The setting of priorities is a complex matter which requires subjective and policy judgments. It is not appropriate to establish a rigid formula or to assign predetermined weight to each factor. The identification of some of the elements is to guide the OSHA staff and inform the public on the development of priorities. It is not intended to create any legal rights with respect to the setting of priorities.

(b) Some factors which may be taken into account in setting priorities for regulating potential occupational carcinogens, when such data are available, are:

(1) The estimated number of workers exposed;

(2) The estimated levels of human exposure;

(3) The levels of exposure to the substance which have been reported to cause an increased incidence of neoplasms in exposed humans, animals or both;

(4) The extent to which regulatory action could reduce not only risks of contracting cancer but also other occupational and environmental health hazards;

(5) Whether the molecular structure of the substance is similar to the molecular structure of another substance which meets the definition of a potential occupational carcinogen;

(6) Whether there are substitutes that pose a lower risk of cancer or other serious human health problems, or available evidence otherwise suggests that the social and economic costs of regulation would be small; and

(7) OSHA will also consider its responsibilities for dealing with other health and safety hazards and will consider the actions being taken or planned by other governmental agencies in dealing with the same or similar health and safety hazards.

§ 1990.133 Publication.

(a) The Secretary shall publish the Candidate List in the **Federal Register** at least annually.

(b) The Secretary shall publish the Priority Lists in the **Federal Register** at least every six months and may seek public comment thereon.

(c) The Secretary may periodically publish in the **Federal Register** a notice requesting information concerning the classification and establishment of priorities for substances on the Candidate List together with a brief statement describing the type of information being sought.

Regulation of Potential Occupational Carcinogens

§ 1990.141 Advance notice of proposed rulemaking.

(a) Within thirty (30) days after OSHA initiates a study concerning the economic and/or technological feasibility of specific standards that might be applied in the regulation of a potential occupational carcinogen, the Secretary will normally publish, in the **Federal Register**, a notice which includes at least the following:

(1) The name of the substance(s),

(2) The scope of the study, including where possible, (i) affected industries, (ii) levels of exposure being studied, (iii) the anticipated completion date of the study;

(3) A brief summary of the available data on health effects;

(4) An estimate of when the Secretary anticipates the issuance of a proposal;

(5) An invitation to interested parties to provide relevant information;

(6) A statement that persons wishing to provide OSHA with their own study should complete it within 30 days after the anticipated proposal date; and

(7) A statement of the procedural requirements that must be met before substantial new issues or substantial new evidence will be considered in the proceeding pursuant to § 1990.145.

(b) Where the Secretary determines to discontinue a feasibility study, the Secretary should publish, within 30 days, a notice in the **Federal Register** so indicating.

§ 1990.142 Initiation of a rulemaking.

Where the Secretary decides to regulate a potential occupational carcinogen, the Secretary shall initiate a rulemaking proceeding in accordance with one of the following procedures, as appropriate.

(a) *Notice of proposed rulemakings (Section 6(b) of the Act).*—(1) *General.* The Secretary may issue a notice of proposed rulemaking in the **Federal Register**, pursuant to Section 6(b) of the Act and Part 1911 of this Chapter. The notice shall provide for no more than a sixty (60) day comment period, and may provide for a hearing, which shall be scheduled for no later than one hundred (100) days after publication of the Notice of Proposed Rulemaking. The commencement of the hearing may be postponed once, for no more than thirty (30) days, for good cause shown.

(2) *Provisions of the proposed standard for Category I Potential Carcinogens.* Whenever the Secretary issues a notice of proposed rulemaking to regulate a substance as a Category I Potential Carcinogen:

(i) The proposed standard shall contain at least provisions for scope and application, definitions, notification of use, a permissible exposure limit, monitoring, regulated areas, methods of compliance including the development of a compliance plan, respiratory protection, protective clothing and equipment, housekeeping, waste disposal, hygiene facilities, medical surveillance, employee information and training, signs and labels, recordkeeping, and employee observation of monitoring as set forth in § 1990.151, unless the Secretary explains why any or all such provisions are not appropriate;

(ii) The model standard set forth in § 1990.151 shall be used as a guideline, and

(iii) The permissible exposure limit shall be set as low as feasible, to be achieved primarily through engineering and work practice controls, except that if a suitable substitute is available for one or more uses, no occupational exposure shall be permitted for those uses.

(3) *Provisions of the proposed standard for Category II Potential Carcinogens.* Whenever the Secretary issues a Notice of Proposed Rulemaking to regulate a substance as a Category II Potential Carcinogen:

(i) The proposed standard shall contain at least provisions for scope and application, definitions, notification of use, monitoring, respiratory protection, protective clothing and equipment, housekeeping, waste disposal, medical surveillance, employee information and training, recordkeeping and employee observation of monitoring as set forth in § 1990.151, unless the Secretary explains why any or all such provisions are not appropriate; and

(ii) The model standard set forth in § 1990.151 shall be used as a guideline; and

(iii) Worker exposure to Category II Potential Carcinogens will be reduced as appropriate and consistent with the statutory requirements on a case-by-case basis in the individual rulemaking proceedings. Any permissible exposure level so established shall be met primarily through engineering and work practice controls.

(b) *Emergency temporary standards.* (Section 6(c) of the Act).

(1) *General.* The Secretary may issue an Emergency Temporary Standard (ETS) for a Category I Potential Carcinogen in accordance with section 6(c) of the Act.

(2) *Grave Danger.* Employee exposure to Category I Potential Carcinogens constitutes a "grave danger" within the meaning of section 6(c) of the Act.

(3) *Provisions of the ETS.* (i) The ETS shall contain at least provisions for scope and application, definitions, notification of use, a permissible exposure limit, monitoring, methods of compliance including the development of a compliance plan, respiratory protection, protective clothing and equipment, housekeeping, waste disposal, medical surveillance, employee information and training, signs and labels, recordkeeping and employee observation of monitoring, unless the Secretary explains why any or all such provisions are not appropriate.

(ii) The model standard set forth in § 1990.152 shall be used as a guideline.

(iii) The permissible exposure limit shall be set as low as feasible through any practicable combination of engineering controls, work practice controls and respiratory protection.

§ 1990.143 General provisions for the use of human and animal data.

Human and animal data which are scientifically evaluated to be positive evidence for carcinogenicity shall be uniformly relied upon for the identification of potential occupational carcinogens. Arguments challenging the following provisions or their application to specific substances will be considered in individual rulemaking proceedings only if the evidence presented in support of the arguments meets the criteria for consideration specified in § 1990.144 or § 1990.145.

(a) *Positive human studies.* Positive results obtained in one or more human epidemiologic studies will be used to establish the qualitative inference of carcinogenic hazards to workers.

(b) *Positive animal studies.* Positive results obtained in one or more experimental studies conducted in one or more mammalian species will be used to establish the qualitative inference of carcinogenic hazard to workers. Arguments that positive results obtained in mammalian species should not be relied upon will be considered only if evidence is presented which meets the criteria for consideration specified in § 1990.144(c) or 1990.144(f).

(c) *Non-positive human studies.* Positive results in human or mammalian studies generally will be used for the qualitative identification of potential occupational carcinogens, even where non-positive results from human studies exist. Such non-positive results will be considered by the Secretary only if the studies or results meet the criteria set forth in § 1990.144(a).

(d) *Non-positive animal studies.* Positive results in one or more mammalian studies will be used for the qualitative identification of potential occupational carcinogens, even where non-positive studies exist in other mammalian species. Where non-positive and positive results exist in studies in the same species, the non-positive results will be evaluated.

(e) *Spontaneous tumors.* Positive results in human or mammalian studies for the induction or acceleration of induction of tumors of a type which occurs "spontaneously" in unexposed individuals will be used for the qualitative identification of potential occupational carcinogens.

(f) *Routes of exposure.* (1) Positive results in studies in which mammals are exposed via the oral, respiratory or dermal routes will be used for the qualitative identification of potential occupational carcinogens, whether tumors are induced at the site of application or distant sites.

(2) Positive results in studies in which mammals are exposed via any route of exposure and in which tumors are induced at sites distant from the site of administration will be used for the qualitative identification of potential occupational carcinogens.

(3)(i) Positive results in mammalian studies in which tumors are induced only at the site of administration, in which a substance or mixture of substances is administered by routes other than oral, respiratory or dermal, will be used as "concordant" evidence that a substance is a potential occupational carcinogen.

(ii) Arguments that such studies should not be relied upon will be considered only if evidence which meets the criteria set forth in § 1990.144(b) is provided.

(g) *Use of high doses in animal testing.* Positive results for carcinogenicity obtained in mammals exposed to high doses of a substance will be used to establish the qualitative inference of carcinogenic hazard to workers. Arguments that such studies should not be relied upon will be considered only if evidence which meets the criteria set forth in § 1990.144(d) is provided.

(h) *"Threshold" or "No-effect" Levels.* No determination will be made that a "threshold" or "no-effect" level of exposure can be established for a human population exposed to carcinogens in general, or to any specific substance.

(i) *Benign tumors.* Results based on the induction of benign or malignant tumors, or both, will be used to establish a qualitative inference of carcinogenic hazard to workers. Arguments that substances that induce benign tumors do not present a carcinogenic risk to

workers will be considered only if evidence that meets the criteria set forth in § 1990.144(e) is provided.

(j) *Statistical evaluation.* Statistical evaluation will be used in the determination of whether results in human, animal or short-term studies provide positive evidence for carcinogenicity, but will not be the exclusive means for such evaluation.

(k) *Carcinogenicity of metabolites.* A substance which is metabolized by mammals to yield one or more potential occupational carcinogens will itself be identified and classified as a potential occupational carcinogen, whether or not there is direct evidence that it induces tumors in humans or experimental animals. Evidence for such metabolism will normally be derived from *in vivo* studies in mammals. In appropriate circumstances, evidence may be derived from *in vitro* studies of mammalian tissues or fractions thereof. Arguments that evidence from *in vivo* metabolic studies in mammals is not relevant to the inference of carcinogenic hazard to humans will be considered only if such evidence meets the criteria set forth in § 1990.144(c).

§ 1990.144 Criteria for consideration of arguments on certain issues.

Arguments on the following issues will be considered by the Secretary in identifying, classifying or regulating any substance pursuant to this Part, if evidence for the specific substance subject to the rulemaking conforms to the following criteria. Such arguments and evidence will be evaluated based upon scientific and policy judgments.

(a) *Non-positive results obtained in human epidemiologic studies.* Non-positive results obtained in human epidemiologic studies regarding the substance subject to the rulemaking or to a similar or closely related substance will be considered by the Secretary only if they meet the following criteria:

Criteria. (i) The epidemiologic study involved at least 20 years' exposure of a group of subjects to the substance and at least 30 years' observation of the subjects after initial exposure;

(ii) Documented reasons are provided for predicting the site(s) at which the substance would induce cancer if it were carcinogenic in humans; and

(iii) The group of exposed subjects was large enough for an increase in cancer incidence of 50% above that in unexposed controls to have been detected at any of the predicted sites.

Arguments that non-positive results obtained in human epidemiologic studies should be used to establish numerical upper limits on potential risks to humans exposed to specific levels of a substance will be considered only if criteria (i) and (ii) are met and, in addition:

(iv) Specific data on the level of exposure of the group of workers are provided, based either on direct measurements made periodically throughout the period of exposure, or upon other data which provide reliable evidence of the magnitude of exposure.

(b) *Tumors induced at site of administration.* Arguments that tumors at the site of administration should not be considered will be considered only if:

(i) The route of administration is not oral, respiratory or dermal; and

(ii) Evidence is provided which establishes that induction of local tumors is related to the physical configuration or formulation of the material administered (e.g., crystalline form or dimensions of a solid material, or matrix of an impregnated implant) and that tumors are not induced when the same material is administered in a different configuration or formula.

(c) *Metabolic differences.* Arguments that differences in metabolic profiles can be used to demonstrate that a chemical found positive in an experimental study in a mammalian species would pose no potential carcinogenic risk to exposed workers will be considered by the Secretary only if the evidence presented for the specific substance subject to the rulemaking meets the following criteria:

Criteria. (i) A complete metabolic profile, including identities of trace metabolites, is presented for the experimental animal species;

(ii) A complete metabolic profile, including identities of trace metabolites, is available for a human population group representative of those who are occupationally exposed;

(iii) Documented evidence is provided for ascribing the carcinogenic activity of the substance in the test animal species to metabolite(s) produced only in that species and not in humans; and

(iv) Documented evidence is provided to show that other metabolites produced also in humans have been adequately tested and have not been shown to be carcinogenic.

(d) *Use of high doses in animal testing.* Arguments that positive results obtained in carcinogenesis bioassays with experimental animals subjected to high doses of a substance are not relevant to potential carcinogenic risks to exposed workers will be considered by the Secretary only if the evidence for the specific substance subject to the rulemaking meets the following criteria:

Criteria. (i) Documented evidence is presented to show that the substance in question is metabolized by the experimental animal species exposed at the dose levels used in the bioassay(s) to metabolic products which include one or more that are not produced in the same species at lower doses.

(ii) Documented evidence is presented to show that the metabolite(s) produced only at high doses in the experimental animal species are the ultimate carcinogen(s) and that the metabolites produced at low doses are not also carcinogenic; and

(iii) Documented evidence is presented to show that the metabolite(s) produced only at high doses in the experimental animal species are not produced in humans exposed to low doses.

(e) *Benign tumors.* The Secretary will consider evidence that the substance subject to the rulemaking proceeding is capable only of inducing benign tumors in humans or experimental animals provided that the evidence for the specific substance meets the following criteria:

Criteria. (i) Data are available from at least two well-conducted bioassays in each of two species of mammals (or from equivalent evidence in more than two species);

(ii) Each of the bioassays to be considered has been conducted for the full lifetime of the experimental animals;

(iii) The relevant tissue slides are made available to OSHA or its designee and the diagnoses of the tumors as benign are made by at least one qualified pathologist who has personally examined each of the slides and who provides specific diagnostic criteria and descriptions; and

(iv) All of the induced tumors must be shown to belong to a type which is known not to progress to malignancy or to be at a benign stage when observed. In the latter case, data must be presented to show that multiple sections of the affected organ(s) were adequately examined to search for invasion of the tumor cells into adjacent tissue, and that multiple sections of other organs were adequately examined to search for tumor metastases.

(f) *Indirect mechanisms.* The Secretary will consider evidence that positive results obtained in a carcinogenesis bioassay with experimental animals are not relevant to a determination of a carcinogenic risk to exposed workers, if the evidence demonstrates that the mechanism by which the observed tumor incidence is effected is indirect and would not occur if humans were exposed. As examples, evidence will be considered that a substance causes a carcinogenic effect by augmenting caloric intake or that the carcinogenic effect from exposure to a substance is demonstrated to be the result of the presence of a carcinogenic virus and it is demonstrated that, in either case, the effect would not take place in the absence of the particular carcinogenic virus or the augmented caloric intake.

§ 1990.145 Consideration of substantial new issues or substantial new evidence.

(a) *Substantial new issues.* Notwithstanding any other provision of

this Part, the Secretary will consider in a rulemaking proceeding on a specific substance any substantial new issues upon which the Secretary did not reach a conclusion in the rulemaking proceeding(s) underlying this Part including conclusions presented in the preamble.

(b) *Substantial new evidence.* Notwithstanding any other provision of this Part, the Secretary will consider in a rulemaking proceeding on a specific substance any arguments, data or views which he determines are based upon substantial new evidence which may warrant the amendment of one or more provisions of this Part. For the purposes of this Part, "substantial new evidence" is evidence directly relevant to any provision of this Part and is based upon data, views or arguments which differ significantly from those presented in establishing this Part, including amendments thereto.

(c) *Petitions for consideration of substantial new evidence.*—(1) *Petition* Any interested person may file a written petition with the Secretary to consider "substantial new evidence" or one or more "substantial new issues" which contains the information specified in paragraph (c)(2) of this section. The Secretary shall treat such a petition as a request to amend this Part, as well as a petition to consider "substantial new evidence".

(2) *Contents.* Each petition for consideration of "substantial new evidence" or one or more "substantial new issues" shall contain at least the following information:

(i) Name and address of the petitioner;

(ii) All of the data, views and arguments that the petitioner would like the Secretary to consider;

(iii) The provision or provisions that petitioner believes are inappropriate or should be added to this Part in light of the new data, views, and arguments;

(iv) A statement which demonstrates that the data, views, and arguments relied upon by petitioners are directly relevant to the substance or class of substances that is the subject of a rulemaking or an Advance Notice of Proposed Rulemaking;

(v) A detailed statement and analysis as to why the petitioner believes that the data, views, and arguments presented by the petitioner:

(A) differ significantly from those presented in the proceeding(s) which establish this Part;

(B) are so substantial as to warrant amendment of this Part; and

(C) constitute a new issue or new evidence within the meaning of paragraphs (a) and (b) of this section.

(3) *Deadline for petitions.* (i) Petitions which comply with paragraph (c) above, shall be filed in accordance with the schedule set forth in the Advanced Notice of Proposed Rulemaking.

(ii) In extraordinary cases the Secretary may consider evidence submitted after the deadline if the petitioner establishes that the evidence relied upon was not available and could not have reasonably been available in whole or substantial part by the deadline and that it is being submitted at the earliest possible time.

(d) *Secretary's response.* (1) The Secretary shall respond to petitions under this paragraph in accordance with § 1990.106.

(2) Whenever the Secretary determines that the "substantial new issue" or the "substantial new evidence" submitted under this paragraph is sufficient to initiate a proceeding to amend this Part, the Secretary shall:

(i) Issue a notice to consider amendment to this Part and not proceed on the rulemaking concerning the individual substance until completion of the amendment proceeding; or

(ii) Issue a notice to consider amendment to this Part and consolidate it with the proceeding on the individual substance.

§ 1990.146 Issues to be considered in the rulemaking.

Except as provided in § 1990.145, after issuance of the advance notice of rulemaking, the proceedings for individual substances under this Part shall be limited to consideration of the following issues:

(a) Whether the substance, group of substances or combination of substances subject to the proposed rulemaking is appropriately considered in a single proceeding;

(b) Whether the substance or group of substances subject to the rulemaking meets the definition of a potential occupational carcinogen set forth in § 1990.103, including whether the scientific studies are reliable;

(c) Whether the available data can appropriately be applied to the substance, group of substances or combination of substances covered by the rulemaking;

(d) Whether information, data, and views that are submitted in accordance with § 1990.144 are sufficient to warrant an exception to this Part;

(e) Whether the data, views and arguments that are submitted in accordance with § 1990.145 are sufficient to warrant amendment of this Part;

(f) Whether the potential occupational carcinogen meets the criteria for a Category I Potential Carcinogen or a Category II Potential Carcinogen.

(g) The environmental impact arising from regulation of the substance;

(h) Any issues required by statute or executive order;

(i) The determination of the lowest feasible level to control exposures to Category I Potential Carcinogens primarily through the use of engineering and work practice controls including technological and economic considerations;

(j) The determination of the appropriate employee exposure level, consistent with the Act's requirements, for Category II Potential Carcinogens;

(k) Whether suitable substitutes are available for one or more uses of Category I Potential Carcinogens and; if so, the no occupational exposure level to be achieved solely with engineering and work practice controls and other issues relevant to substitution; and

(l) Whether the provisions of the proposal and of § 1990.151 and § 1990.152 (model standards) are appropriate, except as limited by § 1990.142 and whether additional regulatory provisions may be appropriate.

§ 1990.147 Final action.

(a) Within one hundred twenty (120) days from the last day of any hearing or ninety (90) days from the close of any post hearing comment period, whichever occurs first, the Secretary shall publish in the **Federal Register:**

(1) A final standard based upon the record in the proceeding; or

(2) A statement that no final standard will be issued, and the reasons therefor, or

(3) A statement that the Secretary intends to issue a final rule, but that he is unable to do so at the present time, including:

(i) The reasons therefor; and

(ii) The date by which the standard will be published, which may not exceed one hundred twenty (120) days thereafter.

(iii) The Secretary may issue no more than one such notice, unless the Secretary determines that (*a*) new evidence which was unavailable during the rulemaking proceeding has just become available; (*b*) the evidence is so important that a final rule could not reasonably be issued without this evidence, and; (*c*) the record is reopened for receipt of comments and/or a hearing on this evidence. This paragraph does not require the Secretary to consider any evidence which is submitted after the dates established for the submission of evidence.

(b) The failure of the Secretary to comply with the required timeframes shall not be a basis to set aside any standard or to require the issuance of a new proposal on any individual substance.

(c) The final standard shall state whether the substance or group of substances subject to the rulemaking is classified as a Category I Potential Carcinogen or as a Category II Potential Carcinogen. If the classification differs from that in the notice of proposed rulemaking, the Secretary shall explain the reasons for the change in classification in the preamble to the final standard.

(d) If the substance is classified as a Category I Potential Carcinogen, the final standard shall conform to the provisions of section 1990.142(a)(2)(iii). If the final standard contains other provisions that substantially differ from the proposed provisions, the Secretary shall explain the reasons for the changes in the preamble to the final standard.

(e) If the substance is classified as a Category II potential carcinogen, the final standard shall conform to the provisions of section 1990.142(a)(3)(iii). If the final standard contains other provisions that substantially differ from the proposed provisions, the Secretary shall explain the reasons for the changes in the preamble to the final standard.

(f) If the substance is classified as a Category II potential carcinogen, the Secretary shall notify the applicable federal and state agencies, including the Administrator of EPA, the Director of NCI, the Director of NIEHS, the Director of NIOSH, the Commissioner of FDA and the Chairperson of CPSC of such determination and request that the applicable agencies engage in, or stimulate, further research pursuant to their legislative authority, to develop new and additional scientific data.

(g) If, after a rulemaking, the Secretary determines that the substance under consideration should not be classified as a Category I potential carcinogen or a Category II potential carcinogen, the Secretary shall publish a notice of this determination in the **Federal Register**, together with the reasons therefor.

Model Standards

§ 1990.151 Model standard pursuant to section 6(b) of the Act.

(a) *Scope and application.*

(1) *General.* This section applies to all occupational exposures to ——— or to (specify those uses or classes of uses of ——— [Chemical Abstracts Service Registry Number 0000] which are covered by the standard, including, where appropriate, the type of exposure to be regulated by the standard) except as provided in paragraph (a)(2).

(2) *Exemptions.* This section does not apply to (insert those uses or classes of uses of ——— which are exempted from compliance with the standard, including, where appropriate,

(i) workplaces where exposure to ——— results from solid or liquid mixtures containing a specified percentage of ——— or less;

(ii) workplaces where another Federal agency is exercising statutory authority to prescribe or enforce standards or regulations affecting occupational exposure to ———; or

(iii) workplaces which are appropriately addressed in a separate standard).

(b) *Definitions.*

"———" means (definition of the substance, group of substances, *or combination of substances, to be regulated*).

"Authorized person" means any person specifically authorized by the employer whose duties require the person to enter regulated areas or any person entering such an area as a designated representative of employees for the purpose of exercising the opportunity to observe monitoring procedures under paragraph (r) of this section.

"Action level" means an airborne concentration of ——— of (insert appropriate level of exposure).

Note.—Where appropriate, consider an action level as a limitation on requirements for periodic monitoring (para. (e)(3)), medical surveillance (para. (n)), training (para. (o)), labels (para. (p)(3)), and other provisions.

"Assistant Secretary" means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee.

"Director" means the Director, National Institute for Occupational Safety and Health, U.S. Department of Health, and Health Services, or designee.

"Emergency" means in any occurrence such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment which may result in a massive release of ——— .

"OSHA Area Office" means the Area Office of the Occupational Safety and Health Administration having jurisdiction over the geographic area where the affected workplace is located.

(c) *Permissible exposure limits provisions.*

(1) *Inhalation.—(i) Time-weighted average limit (TWA).* Within (insert appropriate time period) of the effective date of this section, the employer shall assure that no employee is exposed to an airborne concentration of ——— in excess of: (insert appropriate exposure limit representing: (a) the lowest feasible level, except as modified by paragraph (c)(3) of this section or (b) when it is determined by the Secretary that there are available substitutes for all uses or classes of users that are less hazardous to humans, the proposal shall permit no occupational exposure) as an eight (8)-hour time-weighted average.

Where the Secretary finds that substitutes for ——— may exist, the determination of the lowest feasible level shall include consideration of the availability, practicability, relative degree of hazard, and economic consequences of the substitutes.

(ii) *Ceiling limit.* (*If appropriate.*) Within (insert appropriate time period) of the effective date of this section, the employer shall assure that no employee is exposed to an airborne concentration of ——— in excess of: (insert exposure limit representing the lowest feasible level of exposure as averaged over any: (insert appropriate time period) during the working day.

(2) *Dermal and eye exposure.* (*As appropriate.*) (i) Within (insert appropriate time period) of the effective date of this section, the employer shall (If eye exposure to ——— does not create a risk of cancer, insert exposure level or criteria which will prevent other adverse health effects of eye exposure to ——— if any. If eye exposure creates a risk of cancer, insert exposure level or criteria which represent the lowest feasible level of eye exposure to ———.)

(ii) Within (insert appropriate time period) of the effective date of this section, the employer shall (Insert exposure level or criteria which will prevent other adverse health effects from skin exposure to ———, or which represent the lowest feasible level of skin exposure to ——— or, as appropriate.)

(3) (If appropriate, specify limitations or prohibitions on consumption, storage or use of food, beverages, smoking materials, etc. in certain workplaces.)

(4) *Other restrictions.* The employer shall assure that there is no occupational exposure to ——— from the following uses or classes of uses: (Where the Secretary determines, in the proposal or upon the record of the public rulemaking, that there are available substitutes in certain applications where ——— might otherwise be used, the Secretary here may specify that no occupational exposure to ——— shall be permitted in those circumstances and uses, listing those circumstances or uses. Where the Secretary finds that substitutes for ——— exist, the

determination of their suitability shall include consideration of the availability, practicability, relative degree of hazard, and economic consequences of the substitutes.)

(d) *Notification of use and emergencies.*—(1) *Use.* Within (*insert appropriate time period*), of the effective date of this standard or within thirty days of the introduction of ——— into the workplace, every employer who has a place of employment in which ——— is present shall report the address and location of each place of employment to the OSHA Area Office and an estimate of the number of employees exposed.

(2) *Emergencies.* Emergencies, and the facts obtainable at that time, shall be reported within (insert appropriate number) hours of, or during the first federal working day after, the time the employer becomes aware of the emergency to the OSHA Area Office, whichever is longer. Upon request of the OSHA Area Office, the employer shall submit additional information in writing relevant to the nature and extent of employee exposures and measures taken to prevent future emergencies of a similar nature.

(e) *Exposure monitoring.*—(1) *General.* (i) Determinations of airborne exposure levels shall be made from air samples that are representative of each employee's exposure to ——— over an eight (8) hour period. Monitoring of exposure levels required under this paragraph shall be made as follows: [insert method or alternative methods to be used to meet the requirements of this paragraph].

(ii) For the purpose of this section, employee exposure is that exposure which would occur if the employee were not using a respirator.

(2) *Initial monitoring.* Each employer who has one or more workplaces where (specify the types of workplaces subject to the monitoring requirement) shall, within (insert appropriate period) of the effective date of this section (insert requirements for initial monitoring, as appropriate).

(3) *Frequency.* (Insert, if appropriate, provisions prescribing the minimum frequency at which monitoring must be repeated, the conditions under which such frequency must be increased or may be reduced, and conditions under which such routine monitoring may be discontinued (for example, where the action level is not exceeded). Where appropriate, specify different frequency requirements for certain types of workplaces where, for example, exposure levels are subject to greater or less variability.)

(4) *Additional monitoring.* (Insert, if appropriate, provisions for monitoring, in addition to the requirements (if any) of paragraph (e)(3). This may include a production, process, control or personnel change which might result in new or additional exposure to ———, or whenever the employer has any other reason to suspect a change which might result in new or additional exposures to ———.

(5) *Employee notification.* (i) Within (insert appropriate period) after the receipt of monitoring results, the employer shall notify each employee in writing of the results which represent that employee's exposure.

(ii) Whenever the results indicate that the representative employee exposure exceeds the permissible exposure limits, the employer shall include in the written notice a statement that the permissible exposure limits were exceeded and a description of the corrective action being taken to reduce exposure to or below the permissible exposure limits.

(6) *Accuracy of measurement.* (Insert requirements for accuracy of methods of measurement or detection used to comply with the paragraph).

(f) *Regulated areas.* (1) Within (insert appropriate time period) of the effective date of this section, the employer shall, where practicable, establish regulated areas where ——— concentrations are in excess of the permissible exposure limits.

(2) Regulated areas shall be demarcated and segregated from the rest of the workplace, in any manner that minimizes the number of persons who will be exposed to ———.

(3) Access to regulated areas shall be limited to authorized persons or to persons otherwise authorized by the Act or regulations issued pursuant thereto.

(4) The employer shall assure that in the regulated area, food or beverages are not present or consumed, smoking products are not present or used, and cosmetics are not applied (except that these activities may be conducted in the lunchroom, change rooms and showers required under paragraphs (m)(1)–(m)(3) of this section).

(g) *Methods of compliance.*—(1) *Engineering and work practice controls.* (i) The employer shall institute engineering or work practice controls to reduce and maintain employee exposures to ——— to or below the permissible exposure limits, except to the extent that the employer establishes that such controls are not feasible.

(ii) Engineering or work practice controls shall be implemented to reduce exposures even if they will not be sufficient to reduce exposures to or below the permissible exposure limits.

(2) *Compliance program.* (i) Within (insert appropriate period) of the effective date of this section, the employer shall establish and implement a written program to reduce exposures to or below the permissible exposure limits by means of engineering and work practice controls, as required by paragraph (g)(1) of this section.

(ii) Written plans for these compliance programs shall include at least the following:

(A) A description of each operation or process resulting in employee exposure to ———;

(B) Engineering plans and other studies contemplated or used to determine the controls for each process;

(C) A report of the technology considered or to be considered in meeting the permissible exposure limits;

(D) A detailed schedule for the implementation of engineering or work practice controls; and

(E) Other relevant information reasonably requested by OSHA.

(iii) Written plans for such a program shall be submitted, upon request, to the Assistant Secretary and the Director, and shall be available at the worksite for examination and copying by the Assistant Secretary, the Director, or any affected employee or designated representative.

(iv) The plans required by this paragraph shall be revised and updated periodically to reflect the current status of the program.

(h) *Respiratory protection.*—(1) *General.* The employer shall assure that respirators are used where required pursuant to this section to reduce employee exposures to within the permissible exposure limits and in emergencies. Compliance with the permissible exposure limits may not be achieved by the use of respirators except:

(i) During the time period necessary to install or implement feasible engineering and work practice controls; or

(ii) In work operations in which the employer establishes that engineering and work practice controls are not feasible; or

(iii) In work situations where feasible engineering and work practice controls are not yet sufficient to reduce exposure to or below the permissible exposure limits; or

(iv) In emergencies.

(2) *Respirator selection.* (i) Where respiratory protection is required under this section, the employer shall select and provide at no cost to the employee, the appropriate type of respirator from Table 1 below and shall assure that the employee wears the respirator provided.

Table 1.—Respiratory Protection for ———

(The table will contain a listing of the appropriate type of respirator for various conditions of exposure to ———).

(ii) The employer shall select respirators from those approved by the National Institute for Occupational Safety and Health under the provisions of 30 CFR Part 11.

(3) *Respirator program.* (i) The employer shall institute a respiratory protection program in accordance with 29 CFR 1910.134 (b), (d), (e), and (f).

(ii) Employees who wear respirators shall be allowed to wash their face and respirator facepiece to prevent potential skin irritation associated with respirator use.

(iii) The employer shall assure that the respirator issued to each employee is properly fitted (as appropriate, indicate the requirement for a qualitative or quantitative respirator fit testing program).

(i) *Emergency situations.—(1) Written plans.* (i) A written plan for emergency situations shall be developed for each workplace where ——— is present. Appropriate portions of the plan shall be implemented in the event of an emergency.

(ii) The plan shall specifically provide that employees engaged in correcting emergency conditions shall be equipped as required in paragraph (h) of this section until the emergency is abated.

(2) *Alerting employees.*—(i) *Alarms.* Where there is the possibility of employee exposure to ——— due to the occurrence of an emergency, a general alarm shall be installed and maintained to promptly alert employees of such occurrences.

(ii) *Evacuation.* Employees not engaged in correcting the emergency shall be restricted from the area and shall not be permitted to return until the emergency is abated.

(j) *Protective clothing and equipment.*—(1) *Provision and use.* Where employees are exposed to eye or skin contact with ——— (insert criteria which trigger this requirement as appropriate), the employer shall, within (insert appropriate time period) of the effective date of this section provide at no cost to such employees, and assure that such employees wear, appropriate protective clothing or other equipment in accordance with 29 CFR 1910.132 and .133 to protect the area of the body which may come in contact with ———.

(2) *Cleaning and replacement.* (i) The employer shall clean, launder, maintain, or replace protective clothing and equipment required to maintain their effectiveness.

(k) *Housekeeping.*—(1) *General.* The employer shall, within appropriate time period) of the effective date of this section, implement a housekeeping program to maximize accumulation of ———. (i) The program shall include (insert appropriate elements).

(A) Periodic scheduling of routine housekeeping.

(B) Provision for periodic cleaning of dust collection systems.

(C) Provision for maintaining clean surfaces.

(D) Provision for assigning personnel to housekeeping procedures.

(E) Provision for informing employees about housekeeping program.

(l) *Waste disposal.* (1) *General.* The employer shall assure that no waste material containing ——— is dispersed into the workplace, to the extent practicable.

(2) The employer shall label, or otherwise inform employees who may contact waste material containing ———, the contents of such waste material.

(3) (Insert specific disposal methods, as appropriate.)

(m) *Hygiene facilities and practices.* Where employees are exposed to airborne concentrations of ——— in excess of the permissible exposure limits specified in paragraph (c)(1), or where employees are required to wear protective clothing or equipment pursuant to paragraph (j) of this section, or where otherwise found to be appropriate, the facilities required by 29 CFR 1910.141 shall be provided by the employer for the use of those employees and the employer shall assure that the employees use the facilities provided. In addition, the following additional facilities or requirements may be mandated.

[Specify as appropriate additional facilities and practices such as]:

(1) *Change rooms.* The employer shall provide clean change rooms in accordance with 29 CFR 1910.141(e).

(2) *Showers.* (i) The employer shall provide shower facilities in accordance with 29 CFR 1910. 141(d)(3).

(ii) In addition, the employer shall also assure that employees exposed to ——— shower at the end of the work shift.

(3) *Lunchrooms.* (as appropriate) Whenever food or beverages are consumed in the workplace, the employer shall provide lunchroom facilities which have a temperature controlled, positive pressure, filtered air supply, and which are readily accessible to empoyees exposed to ———.

(n) *Medical surveillance.*—(1) *General.* (i) Within (insert appropriate period) of the effective date of this section, the employer shall institute a program of medical surveillance for (specify the types of employees subject to the medical surveillance requirement, for example, by specifying the level, duration, and frequency of exposure to ——— which make medical surveillance feasible and appropriate for individual employees). The employer shall provide each such employee with an opportunity for medical examinations and tests in accordance with this paragraph.

(ii) The employer shall assure that all medical examinations and procedures are performed by or under the supervision of a licensed physician, and shall be provided without cost to the employee.

(2) *Initial examinations.* At the time of initial assignment, or upon institution of the medical surveillance program, the employer shall provide each employee specified in paragraph (n)(1) of this section an opportunity for a medical examination, including at least the following elements:

(i) A work history, a medical history, and a physical examination with direct emphasis towards (insert specific bodily organs or systems), and shall include the personal history of the employee, family, and occupational background. (Specify additional factors to be considered, including, as pertinent to the specific health hazard(s) posed by ———, genetic and environmental factors.)

(ii) The medical examination shall also include the following: (insert appropriate medical protocol. Where appropriate, provide that the examining physician shall conduct such examinations and tests as are needed according to his professional judgment).

Note.—Where appropriate, require or permit different medical protocols, or different frequencies of medical examinations, for separate sub-populations of employees covered under paragraph (n)(1).

(3) *Periodic examinations.* (i) The employer shall provide the examinations specified below at least (insert appropriate time) for all employees specified in paragraph (n)(1) of this section: (insert appropriate medical protocol for periodic examinations).

(ii) If an employee has not had the examinations prescribed in paragraph (n)(2) of this section within (insert appropriate time period) prior to termination of employment, the employer shall make such examination available to the employee upon such termination.

(4) *Additional examinations.* If the employee for any reason develops signs or symptoms commonly associated with exposure to ———, the employer shall

provide appropriate examination and emergency medical treatment.

(5) *Information provided to the physician.* The employer shall provide the following information to the examining physician:

(i) A copy of this standard and its appendices;

(ii) A description of the affected employee's duties as they relate to the employee's exposure;

(iii) The employee's representative exposure level;

(iv) The employee's anticipated or estimated exposure level (for preplacement examinations or in cases of exposure due to an emergency);

(v) A description of any personal protective equipment used or to be used; and

(vi) The names and addresses of physicians who, under the sponsorship of the employer, provided previous medical examinations of the affected employee, if such records are not otherwise available to the examining physician.

(6) *Physician's written opinion.* (i) The employer shall obtain a written opinion from the examining physician which shall include:

(A) The physician's certification that he has received the information from the employer required under the paragraph (n)(5) and has performed all medical examinations and tests which are in his opinion appropriate under this standard;

(B) The physician's opinion as to whether the employee has any detected medical condition which would place the employee at an increased risk of material impairment of the employee's health for exposure to ———;

(C) Any recommended limitations upon the employee's exposure to ——— or upon the use of protective clothing and equipment such as respirators; and

(D) A statement that the employee has been informed by the physician of the results of the medical examination and any medical conditions which require further examination or treatment.

(ii) The employer shall instruct the physician not to reveal in the written opinion specific findings or diagnoses unrelated to occupational exposure to ———;

(iii) The employer shall provide a copy of the written opinion to the affected employee.

(o) *Employee Information and Training.*—(1) *Training Program.* (i) Within (*insert appropriate period*) of the effective date of this section, the employer shall institute a training program for all employees who (specify the employees subject to the training requirement), and shall require their participation in the training program.

(ii) The training program shall be provided at the time of initial assignment, or upon institution of the training program, and at least (insert appropriate time period) thereafter, and the employer shall assure that each employee is informed of the following:

Note.—Specify, as appropriate, some or all of the following information, or any other appropriate information.

(A) The information contained in the Appendices;

(B) The quantity, location, manner of use, release or storage of ——— and the specific nature of operations which could result in exposure to ———, as well as any necessary protective steps;

(C) The purpose, proper use, and limitations of respirators;

(D) The purpose and a description of the medical surveillance program required by paragraph (n) of this section;

(E) The emergency procedures developed, as required by paragraph (i) of of this section;

(F) The engineering and work practice controls, their function and the employee's relationship thereto; and

Note.—Where appropriate, require training programs with different contents, or different frequencies, for separate subpopulations of the employees specified in paragraph (o)(1).

(G) A review of this standard.

(2) *Access to training materials.* (i) The employer shall make a copy of this standard and its appendices readily available to all affected employees.

(ii) The employer shall provide, upon request, all materials relating to the employee information and training program to the Assistant Secretary and the Director.

(p) *Signs and labels.*—(1) *General.* (i) The employer may use labels or signs required by other statutes, regulations, or ordinances in addition to, or in combination with, signs and labels required by this paragraph.

(ii) The employer shall assure that no statement appears on or near any sign or label, required by this paragraph, which contradicts or detracts from the meaning of the required sign or label.

(2) *Signs.* (i) The employer shall post signs to clearly indicate all workplaces where ——— may be present or where exposures exceed the action level. The signs shall bear the following legend:

DANGER

———

(insert appropriate trade or common names)

CANCER HAZARD

AUTHORIZED PERSONNEL ONLY

(ii) The employer shall assure that signs required by this paragraph are illuminated and cleaned as necessary so that the legend is readily visible.

(iii) Where airborne concentrations of ——— exceed the permissible exposure limits, the signs shall bear the additional legend: "Respirator Required"

(3) *Labels.* (i) The employer shall assure that precautionary labels are affixed to all containers of ——— and of products containing ———, and that the labels remain affixed when the ——— or products containing ——— are sold, distributed or otherwise leave the employer's workplace.

(ii) The employer shall assure that the precautionary labels required by this paragraph are readily visible and legible. The labels shall bear the following legend:

DANGER

CONTAINS ———

CANCER HAZARD

(q) *Recordkeeping*—(1) *Exposure monitoring.*

(i) The employer shall establish and maintain an accurate record of all monitoring required by paragraph (e) of this section.

(ii) This record shall include:

(A) The dates, number, duration, and results of each of the samples taken, including a description of the samples taken, including a description of the sampling procedure used to determine representative employees exposure;

(B) A description of the sampling and analytical methods used;

(C) Type of respiratory protective devices worn, if any; and

(D) Name, social security number and job classification of the employee monitored and of all other employees monitored and of all other employees whose exposure the measurement is intended to represent.

(iii) The employer shall maintain this record for (insert appropriate period) or for the duration of employment plus (insert appropriate period) whichever is longer.

(2) *Medical surveillance.* (i) The employer shall establish and maintain an accurate record of each employee subject to medical surveillance as required by paragraph (n) of this section.

(ii) This record shall include:

(A) A copy of the physicians' written opinions;

(B) Any employees medical complaints related to exposure to ———;

(C) A copy of the information provided to the physician as required by paragraph (n)(6) of this section; and

(D) A copy of the employee's work history.

(iii) The employer shall assure that this record be maintained for (insert appropriate period) or for the duration of employment plus (insert appropriate period) whichever is longer.

(3) *Availability.* (i) The employer shall assure that all records required to be maintained by this section be made available upon request to the Assistant Secretary and the Director for examination and copying.

(ii) The employer shall assure that employee exposure measurement records, as required by this section, be made available, upon request, for examination and copying to the affected employee, former employee, or designated representative.

(iii) The employer shall assure that employee medical records required to be maintained by this section, be made available, upon request, for examination and copying, to the affected employee or former employee, or to a physician designated by the affected employee, former employee, or designated representative.

(4) *Transfer of records.* (i) Whenever the employer ceases to do business, the successor employer shall receive and retain all records required to be maintained by this section.

(ii) Whenever the employer ceases to do business and there is no successor employer to receive and retain the records for the prescribed period, these records shall be transmitted to the Director.

(iii) At the expiration of the retention period for the records required to be maintained pursuant to this section, the employer shall transmit these records to the Director.

(r) *Observation of monitoring.*

(1) *Employee observation.* The employer shall provide affected employees, or their designated representatives, an opportunity to observe any monitoring of employee exposure to ——— conducted pursuant to paragraph (e) of this section.

(2) *Observation procedures.*

(i) Whenever observation of the monitoring of employee exposure to ——— requires entry into an area where the use of protective clothing or equipment is required, the employer shall provide the observer with personal protective clothing or equipment required to be worn by employees working in the area, assure the use of such clothing and equipment, and require the observer to comply with all other applicable safety and health procedures.

(ii) Without interfering with the monitoring, observers shall be entitled to:

(A) Receive an explanation of the measurement procedures;

(B) Observe all steps related to the measurement of airborne concentrations of ——— performed at the place of exposure; and

(C) Record the results obtained.

(s) *Effective date.* This section shall become effective (insert effective date).

(t) *Appendices.* The information contained in the appendices is not intended, by itself, to create any additional obligations not otherwise imposed or to detract from any existing obligation.

Appendix A—Substance Safety Data Sheet

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Appendix B—Substance Technical Guidelines

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Appendix C—Medical Surveillance Guidelines

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§ 1990.152 Model emergency temporary standard pursuant to section 6(c).

Occupational Exposure to ———; Emergency Temporary Standard

§ 1910.1000 ———

(a) *Scope and Application.* (1) *General.* This section applies to all occupational exposures to ———, or to (specify the uses of classes of uses of ——— [Chemical Abstracts Service Registry Number 00000], which are covered by the standard, including, where appropriate, the type of exposure to be regulated by the standard) except as provided in paragraph (a)(2).

(2) *Exemption.* This section does not apply to (insert those uses or classes of uses of ——— which are exempted from compliance with the standard, including, whose appropriate,

(i) workplaces where exposure to ——— results from solid or liquid mixtures containing a specified percentage of ——— or less;

(ii) workplaces where another Federal agency is exercising statutory authority to prescribe or enforce standards or regulations affecting occupational exposure to ——— or

(iii) workplaces which are appropriately addressed in a separate standard.

(b) *Definitions.* "———" means (definition of the substance, group of substances, or combination of substances, to be regulated).

"Authorized person" means any person specifically authorized by the employer whose duties require the person to enter a regulated area or any person entering such an area as a designated representative of employees exercising the opportunity to observe monitoring procedures under paragraph (r) of this section.

"Action level" means an airborne concentration of ——— of (insert appropriate level of exposure).

[Note: where appropriate, consider an action level as a limitation on requirements for periodic monitoring (para. (e)(3)), medical surveillance (para. (n)), training (para, (o)), and other provisions.]

"Assistant Secretary" means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee.

"Director" means the Director, National Institute for Occupational Safety and Health, U.S. Department of Health, Education and Welfare, or designee.

"Emergency" means any occurrence such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment which may result in a massive release of ———.

"OSHA Area Office" means the Area Office of the Occupational Safety and Health Administration having jurisdiction over the geographic area where the affected workplace is located.

(c) *Permissible exposure limits.*—(1) *Inhalation.* (i) Time-weighted average limit (TWA). Within (insert appropriate time) from the effective date of this emergency temporary standard, the employer shall assure that no employee is exposed to an airborne concentration of ——— in excess of: (insert appropriate exposure limit representing the lowest feasible level that can be complied with immediately) as an eight (8)-hour time-weighted average.

(ii) Ceiling limit. (If appropriate.) The employer shall assure that no employee is exposed to an airborne concentration of ——— in excess of: (insert appropriate exposure limit representing the lowest feasible level that can be complied with immediately) as averaged over any: (insert appropriate time period) during the working day.

(2) *Dermal and eye exposure.* (As appropriate.) The employer shall assure that no employee is exposed to eye contact or skin contact with ———.

(i) Within (insert appropriate time period) of the effective date of this section, the employer (If eye exposure to ——— does not create a risk of cancer, insert exposure level or criteria which will prevent other adverse effects of eye exposure to ———, if any. If eye exposure creates a risk of cancer, insert exposure level or criteria which represent the lowest feasible level of eye exposure to ———.

(ii) Within (insert appropriate time period) of the effective date of this section, the employer shall (Insert exposure level or criteria which will prevent other adverse health effects from skin exposure to ———, or which respresent the lowest feasible level of skin exposure to ———, as appropriate.)

(3) (If appropriate, specify limitations or prohibitions on consumption, storage or use of food, beverages, smoking materials, etc. in certain workplaces.)

(d) *Notification of Use.* Within (insert appropriate time) of the effective date of this section, or within fifteen (15) days following the introduction of ——— into the workplace, every employer shall report the following information to the nearest OSHA Area Office for each such workplace:

(1) The address and location of each workplace in which ——— is present;

(2) A brief description of each process or operation which may result in employee exposure to ———;

(3) The number of employees engaged in each process or operation who may be exposed ——— and an estimate of the frequency and degree of exposure that occurs; and

(4) A brief description of the employer's safety and health program as it relates to limitation of employee exposure to ———;

(e) *Exposure monitoring.* (1) *General.* (i) Determinations of airborne exposure levels shall be made from air samples that are representative of each employee's exposure to ——— over an eight (8) hour period. Monitoring of exposure levels required under this paragraph shall be made as follows: [insert method or alternative methods to be used to meet the requirements of this paragraph].

(ii) For the purposes of this section, employee exposure is that exposure which would occur if the employee were not using a respirator.

(2) *Initial monitoring.* Each employer who has one or more workplaces where (specify the types of workplaces subject to the monitoring requirement), shall within (insert appropriate period) of the effective date of this section (insert requirements for initial monitoring, as appropriate).

(3) *Frequency.* (Insert, if appropriate, provisions prescribing the minimum frequency at which monitoring must be repeated, the conditions under which such frequency must be increased, or may be reduced, and conditions under which such routine monitoring may be discontinued (for example where the action level is not exceeded) where appropriate, specify different frequency requirements for certain types of workplaces where, for example, exposure levels are subject to greater or less variability.)

(4) *Additional monitoring.* (Insert, if appropriate, provisions for monitoring, in addition to the requirements (if any) of paragraph (e)(3). This may include a production, process, control or personnel change which might result in new or additional exposure to ——— or whenever the employer has any other reason to suspect a change which might result in new or additional exposures to ———.)

(5) *Employee notification.* (i) Within (insert appropriate period) after the receipt of monitoring results, the employer shall notify each employee in writing of the results which represent that employee's exposure.

(ii) Whenever the results indicate that the representative employee exposure exceeds the permissible exposure limits, the employer shall include in the written notice a statement that permissible exposure limits were exceeded and a description of the corrective action being taken to reduce exposure to or below the permissible exposure limits.

(6) *Accuracy of measurement.* (Insert requirements for accuracy of methods of measurement or detection used to comply with the paragraph.)

(f) *(Reserved.)*

(g) *Methods of compliance.* (i) *General.* Employee exposures to ——— shall be controlled to or below the permissible exposure limits by any practicable combination of engineering controls, work practices and personal protective devices and equipment, during the effective period of this emergency temporary standard.

Note.—Where engineering controls or work practices can reduce employee exposures to ——— it is recommended that they be implemented where practicable, even where they do not themselves reduce exposures to, or below the permissible exposure limits. Work practices which can be implemented by the employer to help reduce employee exposures to ——— include limiting access to work areas to authorized personnel, prohibiting smoking and consumption of food and beverages in work areas, and establising good maintance and housekeeping practices, including the prompt clean-up of spills and repair of leaks.

(2) *Engineering and work practice control plan.* (i) Within (insert appropriate time period) of the effective date of this emergency temporary standard, the employer shall develop a written plan describing proposed means to reduce employee exposures to the lowest feasible level solely by means of engineering and work practice controls (which will be eventually required by a permanent standard for occupational exposure to ———, issued pursuant to section 1990.160(g) of this subpart).

(ii) Written plans required by this paragraph shall be submitted, upon request, to the Assistant Secretary and the Director and shall be available at the worksite for examination and copying by the Assistant Secretary, the Director, and any affected employee or designated representative.

(h) *Respiratory protection.* (1) *Required use.* The employer shall assure that respirators are used where required pursuant to this section to reduce employee exposures to within the permissible exposure limits and in emergencies.

(2) *Respirator selection.* (i) Where respiratory protection is required under this section, the employer shall select and provide at no cost to the employee, the appropriate respirator from Table 1 below and shall assure that the employee wears the respirator provided.

Table 1.—Respiratory Protection for ———

* * * * *

(The table will contain a listing of the appropriate type of respirator for various conditions of exposure to ———.)

(ii) The employer shall select respirators from those approved by the National Institute for Occupational Safety and Health under the provisions of 30 CFR Part 11.

(3) *Respirator program.* (i) The employer shall institute a respirator protection program in accordance with 29 CFR 1910.134 (b), (d), (e) and (f).

(ii) Employees who wear respirators shall be allowed to wash their face and respirator face piece to prevent potential skin irritation associated with respirator use.

(iii) The employer shall assure that the respirator issued to each employee is properly fitted (as appropriate, indicate the requirement for a qualitative or quantitative respirator fit testing program.)

(i) (Reserved.)

(j) *Protective clothing and equipment.* (1) *Provision and use.* Where employees are exposed to eye or skin contact with ——— (insert criteria which trigger this requirement as appropriate), the employer shall within (insert appropriate time period) of the effective date of this standard provide, at no cost to the employees, and assure that employees wear, appropriate protective clothing or other equipment in accordance with 29 CFR 1910.132 and 133 to protect the area of the body which may come in contact with ———.

(2) *Cleaning and replacement.* (i) The employer shall clean, launder, maintain, or replace protective clothing and equipment required by this paragraph, as needed to maintain their effectiveness.

(k) *Housekeeping.*

(1) *General.* The employer shall, within (insert appropriate time period) of the effective date of this section, implement a housekeeping program to minimize accumulations of ———.

(i) The program shall include (insert appropriate elements):

(A) Periodic scheduling of routine housekeeping procedures;

(B) Provision for periodic cleaning of dust collection systems;

(C) Provision for maintaining clean surfaces;

(D) Provision for assigning personnel to housekeeping procedures; and

(E) Provision for informing employees about housekeeping program.

(l) *Waste disposal. (1) General.* The employer shall assure that no waste material containing ——— is dispersed into the workplace, to the extent practicable.

(2) The employer shall label, or otherwise inform employees who may contact waste material containing ——— of the contents of such waste material.

(3) (Insert specific disposal methods, as appropriate.)

(m) *(Reserved).*

(n) *Medical surveillance.* (1) *General.* (i) The employer shall institute a program of medical surveillance for each employee who is or will be exposed to ———. The employer shall provide each such employee with an opportunity for medical examinations and tests in accordance with this paragraph.

(ii) The employer shall assure that all medical examinations and procedures are performed by or under the supervision of a licensed physician, and shall be provided without cost to the employee.

(2) *Initial examinations.* Within (insert appropriate time period) of the effective date of this section, or thereafter at the time of initial assignment, the employer shall provide each affected employee an opportunity for a medical examination, including at least the following elements:

(i) A work history, a medical history, and a physical examination with direct emphasis towards (insert appropriate systems) which shall include the relevant personal history of the employee, family, and occupational background. (Specify additional factors to be considered, including, as pertinent to the specific health hazard(s) posed by ——— genetic and environmental factors.)

(ii) The medical examination shall also include the following: (insert appropriate medical protocol. Where appropriate, provide that the examining physician shall conduct such examinations and tests as are needed according to his professional judgement).

[Note: Where appropriate, require or permit different medical protocols, or different frequencies of medical examinations, for separate sub-populations of employees covered under paragaph (n)(1)].

(3) *Periodic examinations.* (Insert appropriate medical protocol and time.)

(4) *Interim examinations.* If the employee for any reason develops signs or symptoms commonly associated with exposure to ———, the employer shall provide appropriate examination and emergency medical treatment.

(5) *Information provided to the physician.* The employer shall provide the following information to the examining physician:

(i) A copy of this emergency temporary standard and its appendices;

(ii) A description of the affected employee's duties as they relate to the employee's exposure;

(iii) The employee's representative exposure level;

(iv) A description of any personal protective equipment used or to be used; and

(v) The names and addresses of physicians who, under the sponsorship of the employer, provided previous medical examinations of the affected employee, if such records are not otherwise available to the examining physician.

(6) *Physician's written opinion.* (i) The employer shall obtain a written opinion from the examining physician which shall include:

(A) The results of the medical tests preformed;

(B) The physician's opinion as to whether the employee has any detected medical condition which would place the employee at an increased risk of material impairment of the employee's health from exposure to ———;

(C) Any recommended limitations upon the employee's exposure to ——— or upon the use of protective clothing and equipment such as respirators; and

(D) A statement that the employee has been informed by the physician of the results of the medical examination and any medical conditions which require further examination or treatment.

(ii) The employer shall instruct the physician not to reveal in the written opinion specific findings or diagnoses unrelated to occupational exposure to ———;

(iii) The employer shall provide a copy of the written opinion to the affected employee.

(o) *Employee information and training.* (1) Training program. (i) Within (insert appropriate time period) from the effective date of this standard, the employer shall institute a training program for all employees where there is occupational exposure to ——— and shall assure their participation in the training program.

(ii) The employer shall assure that each employee is informed of the following:

(A) The information contained in the Appendices;

(B) The quantity, location, manner of use, release, or storage of ——— and the specific nature of operations which could result in exposure to ———, as well as any necessary protective steps;

(C) The purpose, proper use, and limitations of respirators;

(D) The purpose and description of the medical surveillance program required by paragraph (n) of this section; and

(E) A review of this standard.

(2) *Access to training materials.* (i) The employer shall make a copy of this standard and its appendices readily available to all affected employees.

(ii) The employer shall provide, upon request, all materials relating to the employee information and training program to the Assistant Secretary and the Director.

(p) (Reserved.)

(q) *Recordkeeping.*—(1) *Exposure monitoring.* (i) The employer shall establish and maintain an accurate record of all monitoring required by paragraph (e) of this section.

(ii) This record shall include:

(A) The dates, number, duration, and results of each of the samples taken, including a description of the sampling procedures used to determine representative employee exposure;

(B) A description of the sampling and analytical methods used;

(C) Type of respiratory protective devices worn, if any; and

(D) Name, social security number, and job classification of the employee monitored and of all other employees whose exposure the measurement is intended to represent.

(iii) The employer shall maintain this record for the effective period of this emergency temporary standard, and for any additional period required by the permanent standard.

(2) *Medical surveillance.* (i) The employer shall establish and maintain an accurate record for each employee

subject to medical surveillance as required by paragraph (n) of this section.

(ii) This record shall include:

(A) A copy of the physicians' written opinions;

(B) Any employee medical complaints related to exposure to ———;

(C) A copy of the information provided to the physician as required by paragraph (n)(6) of this section; and

(D) A copy of the employee's work history.

(iii) The employer shall assure that this record be maintained for the effective period of this emergency temporary standard, and for any additional period required by the permanent standard.

(3) *Availability.* (i) The employer shall assure that all records required to be maintained by this section be made available upon request, for examination and copying to the affected employee, former employee, or designated representative.

(ii) The employer shall assure that employee exposure measurement records, as required by this section, be made available upon request to the Assistant Secretary and the Director for examination and copying.

(iii) The employer shall assure that employee medical records required to be maintained by this section, be made available, upon request, for examination and copying to the affected employee or former employee, or to a physician designated by the affected employee, former employee, or designated representative.

(r) *Observation of monitoring.* (1) Employee observation. The employer shall provide affected employees, or their designated representatives, an opportunity to observe any monitoring of employee exposure to ——— conducted pursuant to paragraph (e) of this section.

(2) *Observation procedures.* (i) Whenever observation of the monitoring of employee exposure to ——— requires entry into an area where the use of protective clothing or equipment is required, the employer shall provide the observer with personal protective clothing or equipment required to be worn by employees working in the area, assure the use of such clothing and equipment, and require the observer to comply with all other applicable safety and health procedures.

(ii) Without interfering with the monitoring, observers shall be entitled to:

(A) Receive an explanation of measurement procedures;

(B) Observe all steps related to the measurement of airborne concentrations of ——— performed at the place of exposure; and

(C) Record the results obtained.

(s) *Effective date.* This section shall become effective (insert effective date).

(t) *Appendices.* The information contained in the appendices is not intended, itself, to create any additional obligations not otherwise imposed or to detract from any existing obligation.

Appendix—Substance Safety Data Sheet

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Appendix—Substance Technical Guidelines

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Appendix—Medical Surveillance Guidelines

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[FR Doc. 80-2031 Filed 1-18-80; 1:00 pm]
BILLING CODE 4510-26